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Jubilee Editorial

A 50 year perspective: the British Heart Journal

A title lost, but a reputation won

DENNIS M KRIKLER

Editor, *British Heart Journal*

With this issue the *British Heart Journal* reaches its fiftieth year. The title belies the international flavour. Those who founded the journal would have liked to use the title *Heart*, which is to the point, like *Thorax* and *Gut*, other members of the stable of specialist journals published jointly by the *British Medical Journal* and other societies. This makes it especially piquant that the fiftieth anniversary of the *British Heart Journal* coincides with what would have been the 80th anniversary of *Heart*, which was founded by Thomas Lewis in July 1909. On 1 July 1909, the first issue of *Heart* appeared. It was edited and owned by Thomas Lewis, who produced it with the strong encouragement and help of James Mackenzie. A glance through the early volumes of *Heart* shows how well it served its purpose in the years when knowledge of arrhythmias was enhanced by the development of electrocardiography. Until the American Heart Association established the *American Heart Journal* in 1926, *Heart* was the only important cardiac journal published in English. After the American Heart Association parted company with its publishers it established *Circulation*—another one word title. Credit for the first cardiac journal, still in continuous publication, however, belongs to the French, who established the *Archives des Maladies du Coeur* in 1908.

HOW WE LOST HEART

Before the Cardiac Club was established in 1922,¹ *Heart* had a major role in the development of cardiology in Great Britain, and it also published contributions from many parts of the world. Lewis did not transfer editorial control or indeed ownership of *Heart* to the Cardiac Club, which was essentially an informal body; his ownership and very personal direction of *Heart* were always clear.²

Lewis had an idiosyncratic approach to the publication of his journal, which some may feel to have been a reasonable one: after the first issue, it appeared at irregular intervals, whenever he thought he had sufficient good material.³ As his interests moved away from cardiology, and focused on vascular responses in the skin and factors responsible for the appreciation of pain, so did his journal, and in 1933 he changed its title to *Clinical Science*. After Lewis established the Medical Research Society in 1938, he transferred ownership of *Clinical Science* to the Society the following year, but he remained editor of the journal until 1944, completing a term of 25 years.

THE BRITISH CARDIAC SOCIETY

As the need for a more formal organisation of cardiologists became apparent to the members of the Cardiac Club, their first objective once they had established the British Heart Society, was to launch their own journal. During the planning sessions, various titles were considered, including *Heart*. Lewis reluctantly agreed with this choice, but the name had to be abandoned because the publishers of *Clinical Science* proved unwilling to transfer the title.⁴ So the journal was called the *British Heart Journal* and its history has been closely interwoven with that of the British Cardiac Society throughout the years. Indeed, to celebrate the Golden Jubilee of the *British Cardiac Society* in 1987, the *British Heart Journal* reprinted Cowan's note on the Cardiac Club¹ as well as notes by the joint editors, Maurice Campbell and Evan Bedford, together with a series of review editorials on topics that had interested cardiologists during these 50 years.

British Heart Journal



D Evan Bedford, editor 1939-1947



Maurice Campbell, editor 1939-1958



K Shirley Smith, editor 1959-1972



Walter Somerville, editor 1973-1980

PAST AND PRESENT

Since Campbell and Bedford the journal has had only three editors: Shirley Smith, Somerville, and myself. Despite the parochial title the flavour has always been international, and topics have reflected current interests in cardiology. Electrocardiography was discussed extensively at the beginning and congenital heart disease and the consequences of rheumatic fever and the successes of their surgical treatment were conspicuously featured later. Advances in special areas, for example nuclear magnetic resonance imaging, free radicals, gene probes, and atrial natriuretic peptide continue to get close attention, but the clinical flavour has been retained. Peer review is essential to the judgement of submissions, and every effort is made to combine clarity of expression of language with rigorous statistical analysis.⁵

As the *British Heart Journal* enters its 51st year, the editors remember their dependence on readers and contributors and on those who review submissions as well as others who keep a critical eye on

progress. As the pace of knowledge quickens, the journal aims to remain at the forefront, but not at the cost of losing touch with the sound principles established by those who conceived the *British Heart Journal*.

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Editor

DENNIS M KRIKLER has been editor of the *British Heart Journal* since 1981 having previously been an assistant and associate editor. He is senior lecturer in cardiovascular diseases at the Royal Postgraduate Medical School and consultant cardiologist to Hammersmith Hospital, London. His personal links with American cardiology date back to postgraduate training as a visiting fellow to Boston in 1956 and he has been a fellow of the American College of Cardiology since 1971. His special interests include arrhythmias, electrocardiography, and the history of cardiology. In 1984 he gave the international lecture to the American Heart Association and received the Paul Dudley White citation for international achievement in cardiology.

Assistant Editors

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Editorial

Reactive oxygen metabolites and the human myocardium

CHRISTOPHER J BURRELL, DAVID R BLAKE

From the Cardiac and Rheumatology Departments, The London Hospital, London

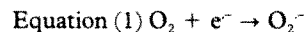
Thrombolytic treatment in acute myocardial infarction achieves coronary patency in most patients.¹ Mortality in groups treated early after the onset of symptoms is significantly reduced,²⁻⁴ but left ventricular function does not always improve.⁵ Myocardial necrosis during the period of vessel occlusion is partly responsible for the irreversible ventricular impairment that occurs even when the vessel is re-opened. In the dog the expanding area of myocardial necrosis induced by experimental coronary occlusion is surrounded by a potentially *viable* ischaemic zone.⁶ But viable ischaemic cells can be irreversibly damaged when coronary flow is re-established. During reperfusion, molecular oxygen is converted to oxygen metabolites, which are toxic and can promote further tissue injury. In this way, re-oxygenation of the myocardium may itself result in secondary deterioration in myocardial function—the “oxygen paradox”.⁷ In animal models the extent of injury is reliably reduced and residual myocardial function appreciably improved by agents that either suppress the generation of oxygen derived free radicals or inhibit the damaging effects that these reactive oxygen metabolites produce.⁸

Direct evidence of injury by free radicals has yet to be shown in the human heart, but many studies of other mammals have linked reactive oxygen metabolites with myocardial injury. Many workers conclude from these studies that interventions directed against free radicals will improve myocardial function after thrombolysis for acute infarction and in other forms of myocardial revascularisation (coronary bypass graft surgery and coronary angioplasty) and during cardiac transplantation. Appreciation of such studies depends on an understanding of some simple biochemistry.

BIOCHEMISTRY OF OXYGEN AND ITS FREE RADICALS

A free radical is an atom, ion, or molecule with one or more unpaired electrons. This configuration leads to an increased reactivity with other molecules. The amount of reactivity depends on the ease with which a species can accept electrons (is reduced) or donate them (is oxidised).

During aerobic metabolism molecular oxygen (O₂) acts as the terminal electron acceptor and undergoes stepwise reduction to water. Oxygen is a bi-radical: it has two unpaired electrons in separate, parallel orbits both spinning in the same direction.⁹ Non-radical species have paired electrons spinning in opposite directions. One of these must spin invert before both can be accepted by oxygen. This process can occur, but limits the reactivity of molecular oxygen, which preferentially accepts electrons one at a time (univalent reduction). The univalent reduction of oxygen produces the superoxide anion radical (O₂^{•-}).



In this equation, the dot (•) represents an unpaired electron and signifies a free radical.

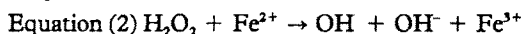
The superoxide anion is comparatively unreactive. It has a very short half life and its solubility in lipids is low. These properties limit its capacity to diffuse away from its site of generation and to affect cell membranes. In an ischaemic environment with acid pH, the anion will become protonated forming the more reactive perhydroxyl radical (HO₂[•]). Because this radical is uncharged, and therefore more lipophilic, it can damage cell membranes.

Because of its electronic configuration the superoxide anion can act both as a reducing agent and an oxidising agent. It can reduce transition metal ions, such as ferric (Fe³⁺) and cupric (Cu²⁺) ions, thereby enabling them to act as catalysts in other free radical reactions.

Further univalent reduction of the superoxide anion yields a non-radical species (O₂²⁻), which exists

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at physiological pH in its protonated form, hydrogen peroxide (H_2O_2). This is less reactive, longer lived, and more lipophilic than the superoxide anion radical (O_2^-). It can diffuse considerable distances from its site of generation and will cross cell membranes. Damage can occur at distant sites via its reduction to the hydroxyl radical ($\text{OH}^\cdot$). It is this reduction reaction (the Fenton reaction) which requires a transition metal ion, such as the ferrous ion (Fe^{2+}) as catalyst.¹⁰



The hydroxyl radical ($\text{OH}^\cdot$) is extremely reactive and has a very short half life. It will react rapidly with most biological substrates, but its damaging effects are localised—it is only likely to modify other molecules within 1–5 molecular diameters of its site of production.¹¹

Radical reactions tend to self perpetuate, producing both the less reactive and the more reactive species. The process terminates only when two radicals collide with each other and interact. Toxicity is affected by the availability of transition metal ions, which catalyse production of the highly reactive hydroxyl ion. It has even been suggested that iron deficiency may protect against myocardial damage in coronary disease.¹²

BIOLOGICAL SOURCES OF FREE RADICALS

While four-electron transfer (tetravalent) reduction of molecular oxygen does occur naturally, and is usually catalysed by the mitochondrial enzyme cytochrome oxidase, several other enzyme systems can reduce molecular oxygen in univalent steps, as described above, and therefore act as sources of reactive oxygen metabolites.

Neutrophils: the respiratory burst

When neutrophils, and other white cell types, are activated two enzyme systems generating free radicals are stimulated: these are the plasma membrane associated nicotinamide adenine dinucleotide phosphate (reduced form) (NAD(P)H) oxidase system and the lysosomally based halide/myeloperoxidase system.¹³ This results in formation of superoxide anion radicals (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl ion ($\text{OH}^\cdot$), and hypochlorous acid (HOCl). These can be detected in the extracellular environment and can promote tissue damage. Activation of white cells occurs in response to many stimuli. These may be particulate (such as bacteria) or non-particulate (such as the protein products of an acute inflammatory reaction—complement, kinin, and cytokines). Neutrophil generation of reactive oxygen metabolites may therefore be relevant to both defence against bacterial infection and to processes involving inflammatory reactions, such as acute myocardial infarction—when neutro-

phils are indeed recruited to the infarct site.

Another consequence of neutrophil activation is the release of proteolytic enzymes, such as elastase, which may enhance tissue damage. Oxygen radicals may indirectly increase elastase activity, because alpha-1-protease inhibitor, which is normally responsible for elastase inactivation, is itself susceptible to oxidative attack.

Endothelial cells

In the capillary endothelial cell (and at other biological sites), the cytosolic enzyme xanthine oxidase is normally present in a dehydrogenase form, using nicotinamide adenine dinucleotide (NAD^+) as an electron acceptor, for the conversion of the purines, hypoxanthine and xanthine, to uric acid. During ischaemia, the dehydrogenase form is converted to the true oxidase form, which uses oxygen, instead of NAD^+ , as electron acceptor. On reperfusion of ischaemic tissue, the delivered oxygen can be reduced by this system, producing superoxide anion radical and hydrogen peroxide.¹⁴

In the myocardium the xanthine oxidase system could be an important source of free radicals,¹⁵ but recent work suggesting that proteolytic conversion into the true oxidase form is rather slow in the heart¹⁶ makes this less likely.

Other sources of free radicals

In addition to the respiratory burst of neutrophils and the cytosolic xanthine oxidase/dehydrogenase system, other important intracellular sources of free radical production include the mitochondria, the endoplasmic reticulum, and the peroxisome.

During ischaemia, components of the mitochondrial electron transport chain become reduced. On re-oxygenation, single electron reduction of oxygen is then more likely and results in increased superoxide production. In addition, enzyme catalysed demethylation and hydroxylation, which are usually coupled to the reduction of NAD(P)H , may become uncoupled after transient ischaemia. Oxygen is then reduced instead of NAD(P)H , with resultant superoxide generation.¹⁷

Finally, free radicals may be generated in association with the arachidonic acid cascade. It may be relevant that during ischaemia, activation of phospholipase increases the release of arachidonate.¹⁸

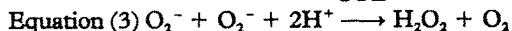
It can be seen that normal cellular metabolism can result in free radical generation and that these intracellular sources may be enhanced during a short lived ischaemic episode. During such adverse conditions normal tissue protection against auto-oxidative tissue damage may be impaired.

BIOLOGICAL PROTECTION AGAINST DAMAGE BY FREE RADICALS

Intracellular superoxide concentrations are kept very

low by the spontaneous "dismutation" of superoxide anion radical to hydrogen peroxide. This reaction may be catalysed by the enzyme superoxide dismutase (SOD).

SOD



Intracellular hydrogen peroxide concentrations are also kept low by its divalent reduction to water, catalysed by the seleno enzyme glutathione peroxidase, and, when hydrogen peroxide concentrations are raised, by the haem centered enzyme catalase. Extracellular concentrations of all these enzymes are low.

Enzymic removal of the hydroxyl radical is precluded by its extreme reactivity. Protection against this radical is dependent on the prevention of its generation or on its scavenging by antioxidants. Scavengers of free radicals are molecules which react with radicals, often producing another radical compound. Antioxidants react to produce less harmful radical species. Naturally occurring antioxidants include α tocopherol (vitamin E), ascorbate (vitamin C), thiols, selenium, and zinc.

Free iron concentrations are kept low by binding to proteins. Intracellular iron is bound to ferritin, and extracellular iron to transferrin and neutrophil derived lactoferrin.

Such compartmentalisation of metal ions is important in reducing random generation of hydroxyl radicals. Hypoxia (by reducing the pH) and xanthine oxidase (by generating the reducing agent superoxide anion radical) may cause decompartmentalisation, and therefore promote metal catalysed oxidative tissue injury.¹⁹

POTENTIAL MECHANISMS OF TISSUE INJURY MEDIATED BY FREE RADICALS

Polyunsaturated fatty acids are found in all cell membranes and they are particularly susceptible to oxidation by free radicals. Rearrangement of the double bond (diene conjugation) gives rise to the formation of lipid peroxides, which in the presence of oxygen participate in an autocatalytic chain reaction. The products of this reaction have a wide range of cytotoxic and pro-inflammatory effects. Protein damage, enzyme release, and oxidation of extracellular lipoproteins may lead to further damaging effects, with spread to adjacent cells.²⁰

INVESTIGATION OF FREE RADICAL MECHANISMS IN THE HEART

Clinical investigation is hampered by the difficulty in directly measuring the ephemeral free radical, especially in complex biological systems.²¹ Specific tissue damage caused by free radicals may be easier to measure. In particular, free radical damage of lipids

and proteins can be assessed.

For example, free radical activity and the extent of tissue damage are related semiquantitatively to the amount of lipid peroxidation. This may be estimated by measuring loss of substrate, uptake of oxygen, diene conjugation, or alkane production. However, the most frequently used assay of lipid peroxidation, the thiobarbituric acid test, has considerable limitations *in vivo*. It lacks specificity, and doubt remains about the interpretation of results.²² Nevertheless, while each method has limitations, where several different methods have been compared there is generally a good correlation.

But the finding of lipid peroxidation in association with a particular disease state cannot be used to implicate free radical damage as a direct *cause* of the disease process, because tissues damaged by any mechanism will peroxidise (go rancid) more rapidly than healthy tissue.²³

Free radical damage to proteins, and especially immunoglobulins, may also be measured, and recently the technique of electron-spin resonance spectroscopy has permitted identification of a free radical in whole tissue, by measurement of the magnetic moment resulting from the spin of its unpaired electron.²⁴

In anaesthetised dogs regional myocardial ischaemia may be induced by ligation of a coronary artery. In these circumstances, concentrations of malondialdehyde (a product of lipid peroxidation) in the coronary venous blood gradually increase with time, reaching a peak at three hours. At the same time, electron-spin resonance spectroscopy of the ischaemic myocardium shows oxygen free radical production. There is depletion of naturally occurring antioxidants, such as α -tocopherol (vitamin E) and ascorbate (vitamin C), and of the enzyme scavengers superoxide dismutase, catalase, and the seleno-enzyme glutathione peroxidase.²⁵

Several recent studies that used a xanthine oxidase/purine system to generate free radicals have confirmed, at least in the rat, the detrimental effects of free radicals on the normal myocardium. There is both reduced contractility²⁶ and ultrastructural change, including swelling of myocytes and endothelial cells, with intracellular disruption.²⁷ Superoxide dismutase and catalase,²⁷ and antioxidants²⁸ have considerable cardioprotective effects.

In animal models, agents that scavenge free radicals may reduce ischaemic injury. Pre-treatment with allopurinol reduces the calculated ischaemic volume below mid-left anterior descending artery ligation,²⁹ and inhibits ischaemic (and reperfusion-induced) arrhythmias.^{15,30,31} While the mechanism of benefit may be a reduction in free radical generation via inhibition of xanthine oxidase, allopurinol is also

a direct scavenger of the hydroxyl radical. However, a vasodilator effect, and maintenance of the nucleotide pool by allopurinol, have also been suggested as possible cardioprotective mechanisms.

Many groups using a range of animal reperfusion models have shown highly significant cardioprotective effects by free radical scavengers such as mannitol (an hydroxyl radical scavenger), scavenging enzymes, antioxidants, and iron chelators such as desferrioxamine. Benefit has been assessed mainly in terms of reduction in infarct size and an improvement in ventricular function in treated as compared with untreated control groups. Appreciable reduction of infarct size was shown by histological and autoradiological techniques,³²⁻³⁴ which estimate the percentage of the "at risk" myocardium that becomes infarcted, and by reduction in creatinine kinase release.^{35,36} Striking improvement in ventricular function, assessed by preservation of developed pressure (dP) and dP/dt max, reduction in end diastolic pressure, and preservation of systolic wall thickening, are also seen in treated groups.³⁷⁻³⁹ Furthermore, the beneficial effects of agents that oppose free radicals are associated with a reduction in free radical production measured directly by electron-spin resonance spectroscopy and indirectly by lipid peroxidation. At the same time, energy stores are increased in the treated, reperfused myocardium.³⁶

The studies showing most improvement were of treatment started before the onset of ischaemia. In clinical situations if treatment is started later during the ischaemic period immediately before reperfusion it may be less beneficial. Furthermore, some studies suggest that intervention directed against free radicals may only delay rather than prevent myocyte necrosis.³⁴

CONCLUSION

The complexity of free radical generation and interaction provides several potential therapeutic targets, and a combined approach that uses xanthine oxidase inhibitors, antioxidants, radical scavengers, and metal chelators is most likely to reduce myocardial reperfusion injury mediated by free radicals in man. Xanthine oxidase inhibitors, allopurinol and oxypurinol, and antioxidants are available. Both recombinant human superoxide dismutase and selenium-based glutathione peroxidase analogues are being developed, and chelators with greater specificity for iron, and which lack the ocular toxicity of desferrioxamine, are being evaluated in animals.

Although free radicals have been implicated in many injurious processes,^{8,20,21} it should be borne in mind that they may also have a beneficial role. Reactive oxygen metabolites are known to be impor-

tant in our natural defence against infection, and may well also initiate tissue repair by, for example, promoting fibroblast proliferation.⁴⁰ Clearly this might be relevant in myocardial scar formation after an infarct.

The future for free radical modification in human heart disease is exciting, but the way forward must lie in careful identification and elucidation of free radical mechanisms in reperfusion injury in man. Only then should suitably controlled clinical trials proceed. We believe that the temptation to administer a theoretically harmless "anti-free radical" cocktail together with thrombolytic treatment for acute myocardial infarction is not yet justified.

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Review

Treatment of pain in acute myocardial infarction

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SUMMARY The treatment of pain in acute myocardial infarction varies with local practice. Narcotic analgesics are still the usual treatment in many hospitals. Knowledge of optimal doses, duration of pain relief, and time between drug administration and pain relief is inadequate. Many studies indicate that the relief of pain is often incomplete after treatment with narcotic analgesics. There is often a need for alternative treatments. Large randomised studies consistently show that β blockade, initially given intravenously and then orally, relieves pain and reduces the need for analgesics. Studies also indicate that early administration of streptokinase and glyceryl trinitrate relieves pain. There is evidence that drugs that limit ischaemic damage also relieve pain.

Chest pain is the most obvious clinical marker of myocardial ischaemia in the acute phase of a suspected acute myocardial infarction. Pain relief is important, not only for patient well being, but also because pain can induce systemic circulatory effects such as an increase in blood pressure, heart rate, and stroke volume. These changes may adversely influence the balance between myocardial metabolic requirement and supply and result in infarct extension. Various treatments have been suggested ranging from pure analgesics, particularly narcotics or tranquillisers, to drugs that have a direct or indirect effect on the ischaemic myocardium.¹⁻³

Narcotic analgesics

DRUGS

The most commonly used agents are morphine, pethidine, pentazocine, methadone, and diamorphine (heroin). Morphine and diamorphine are the most popular because they have been more extensively studied and have better haemodynamic effects than, for example, pentazocine.

RELIEF OF PAIN

The analgesic effect is said to be the result of an increased pain threshold and a reduced sympathetic-adrenal response. Relief of pain in suspected acute myocardial infarction varies considerably. The results depend on how soon after the injection pain

relief is assessed. Since the pain course is difficult to predict, it is difficult to assess whether or not relief or complete disappearance of pain is the result of drug administration. It is said that in many patients relief of pain is unsatisfactory after the administration of morphine⁴⁻⁶ and that narcotics rarely give complete pain relief.^{4,7}

DELAY UNTIL OPTIMAL ANALGESIA

The time lag from drug administration until optimal relief of pain has not been comprehensively assessed. A delay of 20 minutes was reported after intravenous administration and 45-90 minutes after intramuscular administration of analgesics.^{8,9} It is likely that diamorphine and maybe also methadone act somewhat faster than morphine.^{4,10} The effect of diamorphine may be more rapid because it is more soluble in water and so it reaches the circulation more quickly. Its active metabolite, 6-monoacetylmorphine, also quickly passes the blood-brain barrier.

DURATION OF ANALGESIA

The duration of analgesia is difficult to estimate because of the large variability in the course of pain.^{11,12} Postoperative studies suggest that analgesia is effective for seven and nine hours after the administration of 10 and 15 mg morphine respectively.¹³

OPTIMAL DOSES

Little is known about the optimal doses of narcotic analgesics in suspected acute myocardial infarction. Other clinical applications indicate that 7-9 mg of

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morphine/70 kg is optimal and that any further dose increase does not produce greater relief of pain.¹³ In one study 15 mg of morphine given postoperatively resulted in effective pain relief in 83% of patients, whereas 10 mg produced relief in 74%.¹³ Any evaluation of optimal doses of narcotic analgesics must take account of the side effects.

SIDE EFFECTS

Circulatory

When morphine is given to patients who are standing or sitting it induces a drop in blood pressure, most probably by dilatating the capacitance vessels. The unfavourable cardiovascular effects of morphine have been explained by activation of the parasympathetic nervous system. Previously it was suggested that morphine could induce severe hypotension in a high proportion of patients with acute myocardial infarction.¹⁴ But studies showed a significant drop in blood pressure with or without an increase in heart rate in 2–8%.^{15,16} Hypotension has not been shown to be associated with infarct site.¹⁶

Unlike morphine, pentazocine increases the systemic and pulmonary artery pressures, left ventricular filling pressure, systemic vascular resistance, and systolic and diastolic heart volumes and decreases the ejection fraction.^{17,18} Morphine, therefore, seems to protect the myocardium more than pentazocine.

Respiratory

Morphine, diamorphine, pethidine, and pentazocine all induce moderate respiratory changes in acute myocardial infarction including a marginal decrease in pO_2 and a marginal increase in pCO_2 .¹⁰ It has been suggested that diamorphine induces a more rapid but not more pronounced increase in pCO_2 and a more pronounced decrease in pO_2 than morphine. Respiratory insufficiency seems to be rare after treatment with narcotic analgesics in acute myocardial infarction. There was respiratory failure in 1% of patients given morphine and 3% of patients given pethidine in acute myocardial infarction.¹⁵

Central nervous system

Nausea was reported in 20–30% of patients given morphine or pethidine¹⁵ and 5–15% of patients treated with narcotic analgesics vomited.¹⁵ Vertigo occurred in 10–30% of patients.¹⁵ All these symptoms are common in acute myocardial infarction and it is difficult to assess their association with drug treatment.

β Blockers

It is more than 10 years since the first report that intravenous administration of β blockers to selected patients in the early phase of acute myocardial infarction relieved pain within a few minutes, an

effect that persisted for the first hour. In a placebo controlled study by Waagstein and Hjalmarson of practolol, H 87/07 (AB Hässle, Mölndal, Sweden) and metoprolol, three selective blockers two of which (H 87/07 and practolol) had intrinsic stimulatory activity, pain relief occurred within two minutes and the maximum effect was observed within five minutes of the end of intravenous injection. Ten minutes after injection 70% had satisfactory pain relief and after one hour 50% had satisfactory pain relief. Metoprolol (with no intrinsic stimulatory activity) had the most pronounced effect on pain and on heart work. The effect was similar irrespective of whether the infarction was transmural or subendocardial.²

These initial observations have been confirmed in large randomised studies in which more representative patient populations have been studied. Intravenous administration of different β blockers such as propranolol, atenolol, metoprolol, and timolol reduces the pain early,^{19–22} and consumption of analgesics indicates that symptoms of pain are reduced during the next few days if early intravenous treatment is followed by oral treatment.^{20,23,24} In the Göteborg Metoprolol Study of 1395 patients the requirement for analgesics was reduced by 30% during the first four days in the coronary care unit.²³ Similar results were reported by Ramsdale *et al* in a study including 78 patients with suspected acute myocardial infarction.²⁰ Of those who received atenolol intravenously followed by oral treatment, 60% required narcotic analgesics during the next 24 hours compared with 77% of patients given placebo.

In the Metoprolol in Acute Myocardial Infarction on (MIAMI) Trial which included 5778 patients randomised to either metoprolol or placebo treatment,²⁴ the estimated number of hours of pain was reduced by 17%. The number of patients with severe chest pain (defined as pain requiring at least four injections of narcotic analgesics in combination with glyceryl trinitrate and calcium antagonist) was reduced by 42% in the metoprolol group.

SUBGROUP ANALYSIS

In two metoprolol studies the authors assessed the distribution of pain relief in different subgroups.^{23,24} In both the effect was most pronounced in patients with a high initial rate-pressure product. In patients with either a low initial systolic blood pressure (< 120 mm Hg) or a low initial heart rate (< 60 beats/min) the pain course was similar in patients given metoprolol and placebo, as judged by their requirement for analgesics. To some extent this explains why relief of chest pain was better in patients with anterior infarction than in those with inferior infarction.^{23,24} The patients' requirement for analgesics was reduced to a similar extent both in the study in which metoprolol was started very early and in the study in which it was started later.

MECHANISMS OF THE PAIN RELIEVING EFFECT OF β BLOCKADE

There are several possible explanations for the pain relief produced by β blockade in suspected acute myocardial infarction. A reduction in heart work (reduced heart rate, systolic blood pressure, and contractility) improves the relation between coronary perfusion (access of oxygen and nutrients and washout of metabolites) and the myocardial metabolic demand.

A reduction in myocardial metabolic demand reduces the requirement for coronary flow in normal areas, which may cause redistribution of flow to ischaemic areas. In addition, a reduced heart rate prolongs the diastolic perfusion period. In experimental studies in animals, propranolol and metoprolol increased collateral circulation to the ischaemic myocardium.²⁵⁻²⁷

Since it is thought that pain comes only from an ischaemic myocardium, one hypothesis is that pain relief is promoted by reduced ischaemia. The reduction in ST elevation and the rate-pressure product, which were seen in association with pain relief, supports this hypothesis. However, the relation between the decrease in rate-pressure product and the relief of pain after administration of β blockade is not always close. Such observations were reported in angina pectoris and myocardial infarction.^{20,28} Morphine, however, reduces chest pain without changing the level of the ST segment elevation in acute myocardial infarction.²

SIDE EFFECTS

Tolerance of β blockade in suspected acute myocardial infarction has been evaluated extensively in patients with uncomplicated myocardial infarction²⁹ as well as in a more representative patient series.³⁰⁻³² Taking into account the well known cardiovascular contraindications of hypotension, bradycardia, atrioventricular block, severe left heart failure and severe asthma, tolerance was good. On the basis of previous experiences, it seems that about 80% of patients admitted to the coronary care unit because of suspected acute myocardial infarction can be given β blockade in the acute phase. The remaining 20% have absolute contraindications.

OPTIMAL DOSES

The optimal doses of those β blockers that have been evaluated for pain relief in suspected acute myocardial infarction are not yet known. At present, we can only examine the doses used in reported studies. It is possible that many patients who are already receiving long term treatment with β blockers will require higher doses than previously untreated patients because of down regulation of the β receptor.

It may be more appropriate to adjust individual dosage according to heart rate and systolic blood pressure.

Glyceryl trinitrate

It is generally accepted that glyceryl trinitrate administered in the early phase of acute myocardial infarction gives pain relief. The objective evidence for this, however, is not conclusive. The pain relief obtained with repeated sublingual doses of glyceryl trinitrate was compared with that obtained with morphine in 30 patients with acute myocardial infarction.³ Thirteen of 15 patients who received glyceryl trinitrate were free from pain within two hours compared with all of 15 patients receiving morphine. In another study of 30 patients with acute myocardial infarction, intravenous infusion of glyceryl trinitrate gave initial pain relief but the longer term requirement for analgesics was not reduced.³³ In contrast, treatment with intravenous glyceryl trinitrate is known to relieve pain in patients with unstable angina pectoris.^{33,34} In a study of 35 patients, all of whom had angina pectoris at rest which was not responding to β blockers or transdermal or oral glyceryl trinitrate, intravenous infusion of glyceryl trinitrate reduced the mean (SD) number of angina attacks per day from 3.5 (0.4) to 0.3 (0.1) and correspondingly reduced the requirement for sublingual glyceryl trinitrate and for morphine.³⁴

Other treatment alternatives

THROMBOLYSIS

Despite the fact that thrombolytic treatment has been reported to restore blood flow to the ischaemic myocardium there is little information about its effects on pain in the acute phase. Pain relief was reported in one study after early thrombolysis.³⁵ It may be that early thrombolysis gives considerable pain relief in some patients but its effects must be assessed more systematically.

SEDATIVES

It has been reported that levomepromazine has a similar analgesic effect to that of pethidine but with fewer side effects.¹ Mortality over four weeks and one year was significantly lower in patients given levomepromazine than in those treated with pethidine.¹

ANTI-INFLAMMATORY DRUGS

Anti-inflammatory drugs are well tolerated in acute myocardial infarction and do not induce important haemodynamic changes.⁶ Intravenous indoprofen (400 mg) gave better pain relief than intramuscular morphine (10 mg).⁶

NITROUS OXIDE

Nitrous oxide (35%) relieved angina.³⁶ Complete relief of pain was reported in 39% of patients, but the effect was most impressive in patients with mild chest pain. The dose was well tolerated and there were no haemodynamic changes. In Britain, Entonox, a mixture of 50% nitrous oxide with oxygen, is widely used in the ambulance service.³⁷

EPIDURAL AND INTRATHECAL ANAESTHESIA

Intrathecal morphine was effective, with a rapid onset of action and few or no side effects.^{38,39} Epidural administration of morphine was effective in patients in whom intravenous morphine was unsuccessful.^{40,41}

Thoracic epidural sympathetic blockade gave effective pain relief in unstable angina.⁴² Evaluation in acute myocardial infarction is limited.

Patient controlled analgesia

It can be difficult for others to assess a patient's requirement for pain relief. Patient controlled analgesia is most commonly used after operation⁴³ and during child birth.⁴⁴ When the patient presses a button a limited amount of morphine, for example, is infused over a certain interval. The infusion intervals are adjusted for dose, and the patient's age and body weight. This type of treatment has been only occasionally evaluated in acute myocardial infarction.

Optimal use of analgesics

In the coronary care units in Sweden pain relief is usually given by nurses. Their assessment of the severity of pain will determine whether the patient is adequately treated. Bondestam *et al* compared nurses' assessment of pain with that of 47 patients with acute myocardial infarction.⁷ There was a positive correlation between the nurses' and the patients' estimations ($r = 0.76$; $p < 0.001$). The nurses underestimated the patient's pain on 23% of occasions and overestimated it in 20%. Overestimation was more common at higher heart rates and blood pressures. This study also found that patients who said that they had severe pain were not always given pain relief.

Clinical implications

We believe that the initial treatment of pain in acute myocardial infarction should be based on anti-ischaemic drugs.

Patients who present soon after the onset of pain with the electrocardiographic changes of acute infarction, should be given immediate thrombolytic treatment if there are no contraindications. We think

that β blockers should also be given promptly to suitable patients in whom the heart rate is > 50 – 60 beats/min. Although such treatment will reduce pain in many patients, the effect is unpredictable and narcotic analgesics should be given quickly if necessary. We cannot be certain how well patients will tolerate such a combination of treatment but we can recommend it provided there is careful monitoring of the heart rate and systolic blood pressure. If pain continues, a glyceryl trinitrate infusion should probably be started. Subsequent treatment depends on local experience. More experience of the effect of anti-inflammatory drugs, sedatives, and epidural anaesthetics is needed before these alternatives can be widely recommended.

Future aspects

Narcotic analgesics such as morphine will remain the first line treatment of severe pain in acute myocardial infarction, but drugs with a more rapid effect that give better pain relief need to be developed. This in combination with the development of anti-ischaemic drugs should improve the treatment of pain in suspected acute myocardial infarction. Because pain is most intense in the early phase⁴⁵ treatment should be started before the patient is admitted to hospital.

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Quantitative phase analysis in the assessment of coronary artery disease

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SUMMARY The phase image in radionuclide ventriculography shows the timing of ventricular contraction and is valuable in the detection of abnormalities induced by coronary artery disease. The image is usually interpreted subjectively, and in the present study a histogram of left ventricular phase values was used to make interpretation more objective. The left ventricular ejection fraction and the standard deviation, skewness, and kurtosis of the phase histogram were measured at rest, during isometric exercise, and during the final two stages of maximal dynamic exercise in 25 controls and 27 patients with coronary artery disease without previous infarction. The ejection fraction and the standard deviation of the phase had the same predictive accuracy for the presence of disease when measured during the penultimate stage of dynamic exercise (89%) as during the final stage, but their accuracy was lower during maximal exercise (77%) because of motion artefact at high exercise levels. Skewness and kurtosis of the histogram were of no value for the detection of disease, and isometric exercise was of only limited value.

It is concluded that the phase histogram provides an objective measurement of the synchronicity of left ventricular contraction and can increase sensitivity for the detection of abnormality. Data should be acquired at all stages of dynamic exercise, and the penultimate stage should be used if there is any doubt about the validity of the final stage.

Radionuclide ventriculography provides a simple method of assessing global and regional left ventricular function at rest and during exercise. The response of the left ventricular ejection fraction to maximal dynamic exercise has been shown to be useful in the detection of coronary artery disease,¹ although it also has an important role in the assessment of the significance of established disease.^{2,3} An abnormal ejection fraction response is usually the result of regional wall motion abnormalities, which can be assessed objectively using the Fourier phase and amplitude images.⁴ These images are derived from the cineventriculogram and they indicate the timing and magnitude of count changes (hence wall motion) at each point over the heart.

Phase approximates to the time of end systole expressed as a percentage of the total cardiac cycle, and abnormalities occur commonly in coronary artery disease.⁵ The phase image is particularly valuable because abnormalities of the timing of

contraction are difficult to detect by viewing the cineventriculogram alone. The purpose of this work is to investigate the role of quantitative analysis of the phase image as a method of improving upon subjective interpretation. Although quantitative phase analysis has been studied before in patients with coronary artery disease, there are conflicting reports of its value.⁶⁻⁹ The conflict arises partly because of different patient populations and so we have confined this study to patients with known coronary artery disease but without infarction, since these are the patients in whom the question of stress induced left ventricular dysfunction commonly arises. We have also extended the findings of previous studies by comparing the effects of isometric exercise, submaximal dynamic exercise, and maximal dynamic exercise.

Because all parts of the left ventricle should contract with the same timing, the normal left ventricular phase histogram consists of a single narrow peak. Myocardial ischaemia leads to areas of delayed contraction which broaden the peak, and should be reflected in the standard deviation of this histogram. Skewness and kurtosis are other

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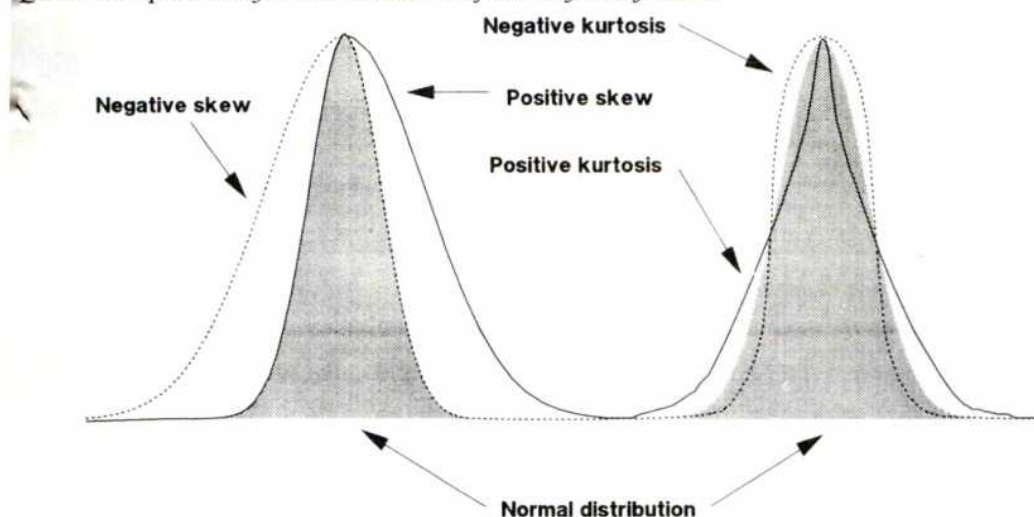


Fig 1 Curves showing positive and negative skewness (left), and positive and negative kurtosis (right). The reference curve (shaded area) is a normal distribution which has zero skewness and kurtosis.

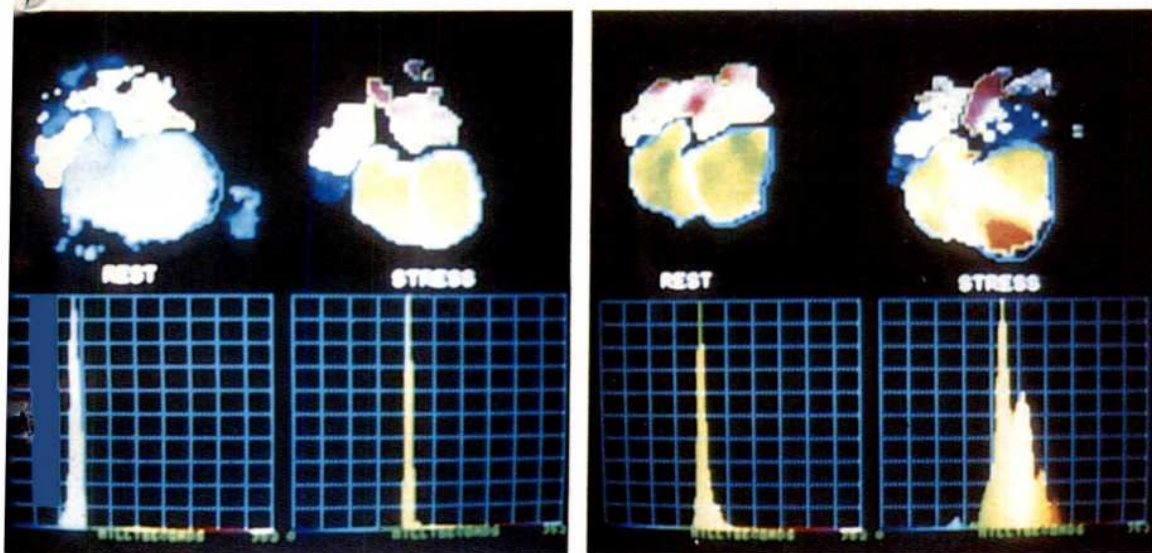


Fig 2 Phase images and histograms at rest and during maximal dynamic exercise in a normal subject (left) and a patient with disease of the left anterior descending coronary artery (right).

parameters of shape that are of potential interest. Skewness is a measure of the symmetry of a distribution, and it is defined as the difference between the mean and the mode expressed as a fraction of the standard deviation.¹⁰

Skew = (mean - mode)/standard deviation

A tail of high values in a distribution produces a skew to the right (positive skewness) and a tail of low

values produces a skew to the left (negative skewness). Kurtosis is a measure of whether a distribution has a wide base with a narrow and sharp peak (leptokurtic) or a relatively narrow base with a flat topped peak (platykurtic) (fig 1). It is calculated from the fourth and second moments of the distribution about its mean (m)¹¹:

$$\text{Kurtosis} = [\mu_4(m)/\mu_2(m)^2] - 3$$

where the n th moment about a point (a) is:

$$\mu_n(a) = \sum_i [(x_i - a)^n] / N$$

When $a = 0$, the first moment about the origin ($\mu_1(0)$) is the mean (m) of the distribution, and when $a = m$, the second moment about the mean ($\mu_2(m)$) is the variance (SD^2).

Patients and methods

Resting equilibrium radionuclide ventriculography was performed in a left anterior oblique projection with 30° of caudal tilt after in vivo erythrocyte labelling with 740 MBq of technetium-99m sodium pertechnetate. A General Electric Portacamera IIC with a 200 mm field of view was used, interfaced to an Informatek Simmis III computer. Sixteen frames per cardiac cycle were acquired with 320 000 counts per frame. Arrhythmia rejection was used to reject data from the cycle following one of length more than 15% from the mean cycle length, which was determined in a 30 second period before acquisition. Premature extrasystoles and the subsequent sinus beat were therefore rejected. Despite this arrhythmia rejection, irregularities of less than 15% of mean cycle length could lead to shortage of counts in the final frames, which if uncorrected would seriously affect the shape of the ventricular count curves and hence the phase values. Each frame was therefore normalised according to the number of cycles contributing to it, the normalisation factor being one, for all but the final one or two frames.

Spatial and temporal smoothing were applied to the data frames. The spatial smooth was a weighted nine point smooth and the temporal smoothing was a weighted three point smooth that was cyclical, so that any discontinuity between frame 16 and frame 1 was minimised. Fourier amplitude and phase images were constructed from the fundamental frequency in each pixel of the smoothed images.

The left ventricular ejection fraction was calculated from count changes within a single fixed left ventricular region of interest that was assigned manually on the end diastolic frame with the aid of the end systolic frame and the amplitude and phase images which assisted with definition of the valve planes. The raw data frames were used for this calculation with an automatic functional background subtraction, which was described by Goris *et al.*¹² This method of background subtraction is operator independent and background counts are calculated from the data frames on the assumption that pixels with positive stroke counts are ventricular pixels and those with zero stroke counts are background. Pixels with negative stroke counts (atria and great vessels)

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are ignored. This method is known to be reliable in patients with good ventricular function (as in all patients in this study) although it may be less accurate in patients with very poor ventricular function.¹²

Isometric exercise was performed by squeezing a partially inflated sphygmomanometer cuff for three minutes at 30% of a previously established maximum pressure, and data were acquired in the final two minutes.

Dynamic exercise was performed by supine subjects on a mechanically braked bicycle. Shoulder restraints, handgrips, and chest straps were used to minimise movement of the chest. Exercise was begun at 25 W and increased in 25 W stages with three minutes at each stage. Data were acquired in the final two minutes of each stage. Patients stopped because of fatigue, pain, or dyspnoea. Important arrhythmia or fall in blood pressure did not occur in any patient.

We studied 25 controls; four were volunteers under the age of 35 without symptoms or signs of heart disease. The remainder were undergoing investigation for suspected cardiac disease but no structural abnormality was found. Fifteen had chest pain and six had electrocardiographic abnormalities, the latter being in aircrew requiring investigation for licensing purposes. They were either repolarisation changes at rest or first or second degree heart block at rest, but none had intraventricular conduction disturbance on the surface electrocardiogram. Investigations included cardiac catheterisation and coronary arteriography in 17. The mean age was 40 (range 22 to 59).

Twenty seven patients with coronary artery disease without previous infarction were also studied. The mean age was 51 (range 30 to 65). Absence of infarction was assumed if there was no history of prolonged chest pain at rest, no Q waves on the electrocardiogram, and a normal x ray left ventriculogram. Cardiac catheterisation and coronary arteriography were performed in all the patients, and disease was considered important if there was a narrowing of $>50\%$ of one of the major coronary arteries or their proximal branches. Two patients had three vessel disease with additional disease of the left main coronary artery, 10 had three vessel disease, 13 had two vessel disease, and two had single vessel disease. The left anterior descending artery was affected in 24, the left circumflex in 22, and the right coronary artery in 18.

The subjects were studied at rest, during isometric exercise, and during the final two stages of a symptom limited dynamic exercise test (later referred to as submaximal and maximal exercise). β Blockade was stopped at least 48 hours before the study and other cardioactive drugs were stopped 12 hours before.

Data were available for all subjects at rest and at maximum exercise but, because some were recruited retrospectively, data during isometric exercise were available in only 12 of the normal subjects and 18 of the patients, and during submaximal exercise in 20 normal subjects and 15 patients. At each stage the following measurements were made: left ventricular ejection fraction; mean left ventricular phase; and the standard deviation, skewness, and kurtosis of the left ventricular phase histogram. The histogram was constructed from the number of pixels within 3° ranges.

Results

EXERCISE DATA

Mean peak exercise level was 155 W (range 125 to 200 W) for the normal subjects and 98 W (range 50 to 175 W) for the patients with coronary artery disease. Eighty five percent of maximal predicted heart rate was achieved in 20 of the 25 controls but in only four of the 27 patients. Dynamic exercise was limited by shortness of breath or fatigue in all of the normal subjects and by chest pain in 14 of the patients, fatigue in six, shortness of breath in three, and claudication in two. No controls and only one patient experienced chest pain during isometric exercise.

Table 1 summarises the haemodynamic changes. The patients with coronary artery disease had a slightly higher resting heart rate than the normal subjects ($p < 0.05$) but at maximal exercise the normal subjects achieved a very much higher rate than the patients ($p < 0.001$). Both groups increased heart rate in response to isometric exercise, and blood pressure increased at all levels of stress. There were no significant differences in blood pressure at any level of stress between the two groups.

Table 1 Mean (SD) of the pulse rate (beats/min) and systolic and diastolic blood pressures (BP) (mm Hg) at rest, during isometric exercise (grip), and during maximal supine dynamic exercise (stress)

	Controls		Coronary artery disease	
	Mean	SD	Mean	SD
Rest:				
Pulse	67.5	9.4	74.9	13.8
Systolic BP	138	8.2	138	22.7
Diastolic BP	89	9.0	93	12.7
Grip:				
Pulse	75.2	7.4	84.2	6.2
Systolic BP	157	11.1	159	26.3
Diastolic BP	103	7.9	105	14.8
Stress				
Pulse	156	21.7	117	19.9
Systolic BP	184	20.5	180	24.2
Diastolic BP	103	13.5	104	15.0

Table 2 Mean (SD) for variables measured at rest, during isometric exercise (grip), and the penultimate (submaximal) and ultimate (maximal) stages of dynamic exercise on the left ventricular phase histogram

	Controls			Coronary artery disease			
	Mean	SD	No	Mean	SD	No	p*
Rest							
EF (%)	64	10.1	25	61	10.2	27	NS
Phase	131	15.3	25	143	18.2	27	<0.01
SD†	8.3	3.5	25	10.6	3.5	27	<0.02
Skewness	-0.11	0.36	25	-0.04	0.52	27	NS
Kurtosis	3.3	3.4	25	4.3	4.6	27	NS
Grip							
EF (%)	66	11.2	12	60	8.2	18	NS
Phase	139	17.6	12	154	18.9	18	<0.05
SD†	7.9	2.2	12	10.7	3.8	18	<0.02
Skewness	-0.06	0.34	12	-0.06	0.39	18	NS
Kurtosis	3.4	2.4	12	2.7	3.2	18	NS
Submaximal exercise							
EF (%)	75	7.2	23	58	12.2	15	<0.001
Phase	153	16.5	20	145	16.6	15	NS
SD†	7.6	2.3	20	15.9	7.30	15	<0.001
Skewness	-0.10	0.45	20	-0.29	0.42	15	NS
Kurtosis	2.2	2.2	20	2.7	3.2	15	NS
Maximal exercise							
EF (%)	73	8.4	25	60	15.4	27	<0.001
Phase	156	16.5	25	153	18.6	27	NS
SD†	8.9	4.3	25	15.3	8.2	27	<0.001
Skewness	-0.08	0.42	25	-0.04	0.44	27	NS
Kurtosis	2.0	3.5	25	2.5	3.5	27	NS
Changes between rest and stress							
Grip.							
EF (%)	2.0	7.2	12	-0.8	6.0	18	NS
SD†	0.6	1.6	12	0.2	2.5	18	NS
Skewness	0.02	0.49	12	0.00	0.63	18	NS
Kurtosis	0.80	2.9	12	-1.6	5.5	18	NS
Submaximal exercise							
EF (%)	11.0	7.4	23	-3.0	7.2	15	<0.001
SD†	0.6	3.1	20	4.4	5.7	15	<0.01
Skewness	0.03	0.50	20	-0.26	0.49	15	NS
Kurtosis	-0.7	2.2	20	-1.3	3.4	15	NS
Maximal exercise							
EF (%)	9.0	10.3	25	-1.0	13.5	27	<0.01
SD†	0.5	4.6	25	4.7	7.4	27	<0.02
Skewness	0.03	0.50	25	0.00	0.50	27	NS
Kurtosis	-1.3	5.0	25	-1.8	5.0	27	NS

*Statistical significance of difference between means for controls and patients with coronary heart disease; †Standard deviation of phase histogram. EF, left ventricular ejection fraction

EJECTION FRACTION

Table 2 shows the ejection fraction and phase histogram data in the two groups. The probability values given are for the differences between the means of the two groups by Student's *t* test. There was no significant difference between the mean resting left ventricular ejection fractions of the two groups at rest, but at submaximal and at maximal dynamic exercise there were large differences. Mean ejection fraction rose from 64% to 73% in the normal subjects ($p < 0.01$) whereas it fell from 61% to 60% in the patients ($p = NS$). If a normal response to dynamic exercise is taken to be an increase in ejection fraction of ≥ 5 percentage units,¹³ the sensitivity, specificity, and predictive accuracy of ejection fraction for the detection of disease were 85%, 68%,

Table 3 Sensitivities, specificities, and predictive accuracies for the detection of coronary artery disease from the response to isometric exercise (grip), submaximal dynamic exercise, and maximal dynamic exercise with the following criteria for normality: change in ejection fraction (EF) $\geq 5\%$, standard deviation (SD) of the phase histogram $\leq 10^\circ$, normal ejection fraction response, and standard deviation.

	Sensitivity	Specificity	Predictive accuracy*
Grip EF	15/18 (83%)	4/12 (33%)	19/30 (63%)
Submaximal EF	13/15 (87%)	21/23 (91%)	34/38 (89%)
Maximal EF	23/27 (85%)	17/25 (68%)	40/52 (77%)
Grip SD	9/18 (50%)	11/12 (92%)	20/30 (67%)
Submaximal SD	13/15 (87%)	18/20 (90%)	31/35 (89%)
Maximal SD	22/27 (81%)	20/27 (74%)	42/54 (78%)
Grip EF + SD	16/18 (89%)	4/12 (33%)	20/30 (67%)
Submaximal EF + SD	15/15 (100%)	16/20 (80%)	31/35 (89%)
Maximal EF + SD	25/27 (93%)	15/27 (56%)	40/54 (74%)

*True positives + true negatives/number of test.

and 77% respectively at maximum exercise and 87%, 91%, and 89% at submaximal exercise (table 3).

PHASE

At rest, the patients with coronary artery disease had a slightly higher mean left ventricular phase and standard deviation of phase than normal ($p < 0.01$ and 0.02 respectively). This is surprising in view of the fact that none of the patients had evidence of previous infarction, but visual inspection of the amplitude and phase images showed definite abnormalities at rest in six patients and possible abnormalities in a further two. The standard deviation of phase was $> 10^\circ$ in 12 patients and in six controls, giving a sensitivity and specificity for the detection of disease at rest of 44% and 24% respectively. These figures are inadequate for the phase image at rest to be useful for the detection of disease, but it can be concluded that phase analysis of the radionuclide ventriculogram is more sensitive than subjective reporting of the x ray contrast ventriculogram in the detection of abnormal ventricular wall motion (the contrast ventriculograms were all considered to be normal).

The mean phase did not differ between the two groups at maximal or submaximal exercise because higher heart rates were achieved in the normal group. There were large differences, however, in the mean standard deviation of phase. This was almost unchanged with exercise in the normal subjects, increasing from 8.4° to 8.9° ($p = \text{NS}$), but in the patients it increased significantly from 10.6° to 15.3° ($p < 0.02$). With an arbitrary criterion for normality for the standard deviation of phase as $\text{SD} \leq 10^\circ$, the sensitivity, specificity, and predictive accuracy for the detection of disease are 81%, 74%, and 78% respectively at maximal exercise, and 87%, 90%, and

Underwood, Walton, Laming, Ell, Emanuel, Swanton 89% at submaximal exercise (table 3). Visual interpretation of the images showed abnormalities in only 17 (63%) of the 27 patients, indicating that quantitative measurement from the image is more sensitive than visual inspection alone.

SKEWNESS AND KURTOSIS

At no stage of exercise (isometric and dynamic) were there any significant changes in skewness or kurtosis in either group, nor were there any differences between the groups.

ISOMETRIC EXERCISE

There were significant differences in mean phase and in the standard deviation of phase between the two groups during isometric exercise, but the means did not change between rest and isometric exercise and these differences reflect the resting abnormalities. In three of the patients, however, the standard deviation of phase was normal at rest but became abnormal during isometric exercise. This did not occur in any of the controls and it suggests that the development of new wall motion abnormalities during isometric exercise is highly specific for the presence of disease.

EXAMPLES

To illustrate the changes described above, fig 2 shows the phase images and phase histogram at rest and at maximal dynamic exercise in a normal subject and in a patient with disease of the left anterior descending coronary artery. The normal subject was a pilot in the Royal Air Force who played regular squash and who had T wave inversion in a resting electrocardiogram. He had a resting bradycardia (55/minute) and the resting phase was low (109°) with a narrow phase histogram ($\text{SD } 6.7^\circ$). On exercise, he reached a peak rate of 172/minute and mean phase increased to 143° , but the phase histogram remained narrow ($\text{SD } 5.2^\circ$). The increase in phase is reflected in the change from blue to green in the display.

The patient had angina without previous myocardial infarction and the resting phase image was normal with mean phase 138° and standard deviation 9.6° (close to the upper limit of normal). On exercise, he reached 125 W before stopping with angina at a rate of 138/minute. The phase image became clearly abnormal with very high values at the apex and a standard deviation of 31° . The phase over the basal part of the ventricle also increased because of the tachycardia. Despite these phase changes, the amplitude image was relatively unchanged.

Discussion

We have shown that the response of the ejection fraction to dynamic exercise is sensitive and specific

in the detection of coronary artery disease, with a predictive accuracy of 89% in the population studied. This accords with the findings of several previous studies.¹⁴⁻¹⁷ We have also shown that the standard deviation of the phase histogram has an equal predictive accuracy if a normal value is taken to be 10° or less. The sensitivity of the phase histogram is not unexpected because the ejection fraction is abnormal because of regional abnormalities of wall motion, which should be reflected in the phase image. The abnormalities were apparent from visual inspection of the phase image alone in 63% of cases, but the quantitative measurement of standard deviation increased sensitivity. This does not imply that the phase image is redundant, rather that the phase image and the phase histogram should be considered together. The histogram does not give any regional information and if the standard deviation of phase is abnormal then the affected area can be localised on the phase image.

There are previous studies of the phase histogram in health and disease. Our findings accord with those of Ratib *et al* who looked at seven controls and 35 patients with coronary artery disease and found that the normal limits of the standard deviation of phase were 12° at rest and 10° during dynamic exercise, with a sensitivity of 95% for the detection of disease.⁶ Eight of the patients, however, had previous myocardial infarction and so this was not a homogeneous group. It is not surprising that a technique that detects abnormalities of ventricular wall motion should be sensitive in detecting disease in patients with infarction.

Vos *et al* studied 75 patients at rest only and tested the ability of quantitative phase analysis to detect regional abnormalities that were seen on the cine display of the radionuclide ventriculogram.⁷ They found the standard deviation of phase to be sensitive but skewness to be unhelpful. Mean normal standard deviation of phase was slightly lower than other studies at 4.7° , which may be explained by the way in which they corrected for heart rate by varying the cycle length. Mean normal skewness was similar to this study at -0.09 .

Norris *et al* studied 17 patients with coronary artery disease without infarction at submaximal and maximal exercise.⁹ They found similar sensitivities of ejection fraction and standard deviation of phase at maximal exercise (53% and 59% respectively) and that combining the two gave a sensitivity of 76%. These figures parallel our own, although the generally lower values reflect the wide range of sensitivities reported for the detection of coronary artery disease.¹⁸ Unfortunately, they do not say what stage of exercise is regarded as submaximal, and it is not possible to compare their submaximal data with our

own.

Our results, however, do not accord with the findings of Turner *et al* who found that the standard deviation of phase was not sensitive in the detection of coronary artery disease but that skewness was.⁸ Mean resting standard deviation of phase was 8.4° with similar changes in controls and those with coronary artery disease, but mean normal skewness at rest was -0.55 (significantly different from this and other studies) decreasing to -0.71 with exercise in controls but increasing to $+0.03$ in coronary artery disease. This discrepancy is difficult to explain unless it is attributable to differing study populations or different methods of calculating phase. To cope with rate related changes in cycle length, Turner *et al* included only the first 500 ms of the cycle if the heart rate was under 120/minute and the whole cycle if it was over 120/minute. This unconventional method of calculating phase is likely to affect findings in a way that is difficult to predict theoretically. Their suggestion that skewness is sensitive in the detection of disease is unexpected. Although a small area of abnormal phase may skew the phase distribution to higher values, a large area of abnormal phase will skew it to low values with the normal values being in the asymmetric tail on the left. The weight of evidence is that neither skewness nor kurtosis is helpful in detecting coronary artery disease.

SUBMAXIMAL EXERCISE

An interesting finding of this study was that the predictive accuracies of both ejection fraction and standard deviation of phase were greater at the stage before maximal exercise than at maximal exercise. It is often considered that maximal exercise is important for high sensitivity of exercise testing in coronary artery disease, but for exercise radionuclide ventriculography this may be counterproductive. Despite measures to immobilise the upper body during exercise, motion artefact will decrease the measured ejection fraction. This effect will be greatest at the higher levels of exercise achieved in the normal subjects and will reduce specificity but have a lesser effect upon sensitivity. Table 3 shows that sensitivity is not reduced at submaximal exercise but that specificity is greatly increased. Schneider *et al* evaluated changes in ejection fraction at each stage of exercise¹⁹ and although they did not analyse their findings in this way, their data show a higher specificity at the stage before maximal exercise (59% v 41%) with only a small reduction in sensitivity (78% v 80%). They do not mention, however, that the "up-down" pattern of ejection fraction may in some cases be artefactual. Their specificity is lower than in the present study but there is a wide range of reported values, which is probably explained by

patient selection. For instance, Schneider *et al* had a much higher number of patients with single vessel disease.

The effect of motion upon the phase image is harder to predict but it may reduce the standard deviation of phase, since any regional abnormality will be spread across the image. This effect may have been seen by Bacharach *et al* who found a direct relation between standard deviation of phase and heart rate in controls.²⁰ While it is not certain that the observation was caused by motion artefact, it seems likely. If motion does reduce the standard deviation of phase, then a lower sensitivity for disease would be expected at maximum exercise, which fits with our observations.

If maximal exercise is not the ideal level for the detection of abnormality, then a compromise has to be chosen at a sufficiently high level for ischaemia to be induced but before the data are degraded by artefact. The operator can best decide at which stage ST segment changes or pain begin and whether there is untoward motion. If appreciable artefact is suspected, an examination of the trend of ejection fraction or wall motion changes at each stage is helpful. If there is a precipitous drop in ejection fraction in the final stage of exercise in a subject who has no other signs of disease, then a lower stage of exercise may be more reliable. Abnormalities of ventricular function occur at an early stage of myocardial ischaemia, and nearly always before the onset of chest pain.^{21,22} The stage before maximal exercise seems to be a suitable compromise in routine practice.

ISOMETRIC EXERCISE

Because of the problem of motion, isometric exercise has been considered an attractive alternative to dynamic exercise, especially for patients with claudication or for those who are unable to exercise for other reasons. The haemodynamic effects of isometric exercise have been studied previously. In healthy individuals, heart rate, blood pressure, and cardiac output increase, whereas left ventricular end diastolic pressure and stroke volume decrease or are unaltered. In patients with coronary artery disease, left ventricular end diastolic pressure increases and there is often a reduction in ejection fraction.²³⁻²⁵ The pressor response seems to be caused by a rate dependent increase in cardiac output with unchanged peripheral vascular resistance.²⁶ In contrast, the cold pressor response is the result of a sympathetically mediated increase in peripheral vascular resistance.²⁷

Unfortunately, our study showed that the changes induced in ejection fraction by isometric exercise are small and in most cases they are inside the limits of reproducibility, which is ± 6 percentage units.²⁸ Whatever the definition of a normal ejection fraction

response, therefore, the test cannot have a high predictive accuracy. New wall motion abnormalities were induced in three patients, and this was highly specific for the presence of disease. Clearly, the phase image is able to detect small changes in regional wall motion that do not produce changes of ejection fraction.

There is some dispute in published reports about the sensitivity of isometric exercise for the detection of coronary artery disease. Early studies by Bodenheimer *et al* found isometric exercise to be 91% sensitive and 87% specific according to the regional ejection fraction image,^{29,30} whereas Peter and Jones found it to have very low sensitivity when the global ejection fraction was used.³¹ The sensitivity of the ejection fraction to cold pressor stress is similarly low.³² The high sensitivity of the regional ejection fraction image is unexpected because it is a method of displaying regional wall motion and most workers agree that the incidence of new abnormalities is low. In our study, for instance, new abnormalities were induced in three (17%) of 18 patients although abnormalities were also present at rest in nine (50%) out of 18. The sensitivity is obviously dependent upon the population studied, and if there is a high incidence of resting abnormalities, the sensitivity of isometric exercise will appear to be high.

THE WEIGHTED HISTOGRAM

The phase histogram used in this study was unprocessed, with all pixels having equal weight. Bacharach *et al* have shown that the effect on the histogram of statistical errors in phase values can be eliminated by error weighting, where the weight that each pixel contributes to the histogram is weighted according to the error calculation of its phase.³³ The error in calculating phase is closely related to the number of counts in the pixel at end diastole. In this way, the range of normal for the standard deviation of phase is reduced and the histogram may be more sensitive in detecting abnormalities. Another technique that may increase sensitivity is "cluster weighting", in which pixels that have surrounding pixels of similar phase are given more weight. The effect of random variations in phase is eliminated and regional abnormalities may be detected more easily.

THE AMPLITUDE IMAGE

Changes in the amplitude image between rest and stress were not considered in this study. Part of the reason is that the amplitude image is usually interpreted visually since, although normal regional values can be established, the range of normal is large. We have seen that visual interpretation of the phase and amplitude images together resulted in a 63% sensitivity for the detection of disease but when

the amplitude image alone was used this fell to 52%. Vos *et al* found that mean amplitude was the most valuable variable for detecting abnormal wall motion, with standard deviation of phase also being an independent predictor.⁷ This was in patients with resting abnormalities, however, and it appears that reversible ischaemia leads to greater abnormalities of phase than of amplitude. In impending myocardial infarction, for instance, areas with delayed contraction but normal amplitude may be salvageable by reperfusion but areas with reduced amplitude are not.³⁴

Figure 2 shows the usual pattern of stress induced ischaemia with a comparatively minor amplitude abnormality despite an obvious phase abnormality, which is the usual pattern. An example of the opposite has been described in a patient with a large stress induced amplitude defect and less important phase abnormalities.³⁵ The conclusion is that while the phase image is very sensitive in the detection of abnormalities of the timing of ventricular wall motion, the extent of wall motion is an independent variable, and the amplitude and phase images should always be interpreted together.

Conclusions

The left ventricular ejection fraction and the standard deviation of left ventricular phase have the same predictive accuracy for the presence of disease when measured during submaximal exercise (89%), but this accuracy is lower at maximal exercise (77%). This reduction is probably the result of motion artefact at high exercise levels, and it leads to reduced specificity (68%) despite maintained sensitivity (85%). Skewness and kurtosis of the phase histogram are of no value in the detection of disease. Isometric exercise is of very limited value for the detection of disease since changes in ejection fraction are small and variable; however, wall motion abnormalities induced by isometric exercise are specific for the presence of disease.

The phase histogram provides an objective measurement of the synchronicity of left ventricular contraction and can increase sensitivity for the detection of abnormality. Data should be acquired at all stages of dynamic exercise, and the penultimate stage should be used if there is any doubt about the validity of the final stage.

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Effects of enalapril on myocardial noradrenaline overflow during exercise in patients with chronic heart failure

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SUMMARY The effects of the angiotensin converting enzyme inhibitor enalapril on myocardial sympathetic tone, as represented by noradrenaline overflow, were studied in 14 men with congestive heart failure (mean ejection fraction 20%) in a double blind crossover comparison with placebo. Arterial and coronary sinus catecholamine concentrations and oxygen content, and coronary sinus blood flow, were measured at rest and during peak symptom limited upright exercise on a bicycle ergometer. There were no significant changes four hours after the first dose of enalapril, but after six weeks of treatment (10-20 mg/day) enalapril reduced myocardial overflow of noradrenaline at peak exercise. The external workload (exercise duration) increased from baseline values after both placebo and enalapril, and there was no difference between placebo and enalapril at six weeks. Heart work, however, was lower after enalapril: stroke work index was reduced at rest and the double product was lower at peak exercise. The reduction in maximal myocardial oxygen consumption after enalapril did not reach statistical significance. Coronary sinus adrenaline concentrations after enalapril and after placebo were not significantly different.

The long term reduction of myocardial sympathetic activity on exercise may represent a significant benefit from angiotensin converting enzyme inhibition in heart failure and may reflect a reduced cardiac workload.

In congestive heart failure the sympathetic drive is increased,¹ as manifest by raised blood concentrations of noradrenaline² in association with reduced myocardial noradrenaline content and down regulation of β_1 receptors.³ Noradrenaline concentrations in the coronary sinus are also raised at rest, suggesting an increased sympathetic drive to the heart in chronic heart failure.^{4,5}

Angiotensin converting enzyme inhibitors have proved beneficial in the treatment of chronic heart failure.⁶⁻¹⁰ There is also evidence that they reduce raised systemic concentrations of noradrenaline^{11,12} and that they may reduce the incidence of ventricular arrhythmias.^{11,13} It is possible that some of their beneficial effects may be mediated through actions on myocardial sympathetic stimulation.

We investigated the short term and long term

effects of the angiotensin converting enzyme inhibitor enalapril on arterial and coronary sinus noradrenaline concentrations at rest and on exercise in patients with heart failure.

Patients and methods

We studied 14 men aged 30-69 (mean (SD) 50.9 (11.5)); 11 had coronary heart disease without evidence of effort related myocardial ischaemia and three had dilated cardiomyopathy. Nine were in New York Heart Association class II and five were in class III. Radionuclide ejection fractions on entry to the study ranged from 10% to 39% (mean (SD) 20 (8)%). All patients were treated with constant doses of digoxin (0.25 (0.09) mg/day) and diuretics (frusemide 114 (123) mg, n = 14; amiloride 8.5 (2.4) mg/day, n = 10) throughout the trial.

All the patients gave written informed consent and completed a 12 week double blind placebo controlled randomised crossover trial. All patients were studied five times, during three separate study days at the

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beginning and end of two six week periods. They were studied first on entry to the trial (baseline data), and thereafter they were randomised to receive enalapril 10 mg orally or matched placebo. Four hours later we measured the short term data. Treatment was continued, and increased after two weeks to enalapril 20 mg/day or placebo two tablets per day, if there were no symptoms suggestive of hypotension or other unwanted effects. After six weeks, patients were studied again four hours after the last dose of enalapril or placebo (long term data), and then given the first dose of the alternative treatment. The protocol was repeated, with short term data being obtained four hours after this dose, and long term data six weeks later at the end of the study and four hours after the last dose. During long term treatment 12 patients received enalapril 20 mg/day and two patients took 10 mg/day.

On each occasion patients completed a maximal symptom limited exercise test on a bicycle ergometer. They had at least two training tests before entry into the study, and the exercise protocol was uniform. The initial workload of 25 W was increased by 25 W every three minutes until exercise was limited by dyspnoea or fatigue. Recordings were made in the same sequence, first at rest (sitting on the bicycle) and then at peak exercise.

Measurements of haemodynamic function and blood samples for estimation of oxygen saturation and adrenaline and noradrenaline concentrations were obtained from a cannula in the radial artery, a Swan Ganz catheter in the pulmonary artery, and a Baim catheter¹⁴ in the coronary sinus; the proximal thermistor and sampling port of the Baim catheter were placed about 2 cm beyond the coronary sinus orifice. A satisfactory coronary sinus catheter position, confirmed by the injection of 5 ml of low osmolar contrast medium, was obtained in 75% of tests. During the measurement of cardiac output we confirmed that in these patients the recordings of the coronary sinus thermistor were not altered by the injection of an ice cold bolus of 5% dextrose into a central vein—this showed that there was no evidence of reflux from the right atrium into this portion of the coronary sinus at rest or on exercise.¹⁵ Previous radiographic studies showed that such catheters were stable during bicycle exercise.¹⁶ After insertion of the catheters, the patients rested for at least one hour before the first measurements.

Blood flow in the coronary sinus was measured with an Elecath Baim coronary flow system (Electro Catheter Corporation) during an infusion of 5% dextrose at 40 ml/minute at room temperature. Plasma catecholamine concentrations were estimated by high pressure liquid chromatography with electrochemical detection.¹⁷ Myocardial overflow of

adrenaline or noradrenaline was calculated as the product of the difference between aortic concentrations of adrenaline or noradrenaline and coronary sinus concentrations, and the coronary sinus plasma flow, which was calculated as: coronary sinus blood flow $\times (1 - \text{venous haematocrit})$. The haematocrit for this last calculation was measured in a venous blood sample taken at rest within 24 hours of the start of each study day. Total body oxygen consumption was calculated as the product of systemic arteriovenous oxygen content difference (in ml/l) and cardiac output (the mean of three separate thermodilution curves) divided by body weight.¹⁸ Myocardial oxygen consumption was calculated as the product of the difference between the aortic and coronary sinus oxygen contents and coronary sinus blood flow. Stroke work was calculated as the product of stroke index (cardiac output divided by heart rate, per m² body surface area) and the difference between the mean systemic arterial and the mean pulmonary capillary wedge pressures.

The results were analysed first according to the method of Hills and Armitage for a crossover trial.¹⁹ There were no significant period or carry over effects on the long term data reported in this study. Baseline data were incomplete in six men because of initial inexperience in coronary sinus catheterisation, but long term treatment data were obtained in most subjects. We therefore report the results of paired *t* tests to compare the long term effects of enalapril with those of placebo. We also used paired *t* tests to compare the long term effects of enalapril or placebo with baseline values.

Short term effects were compared with control data obtained according to the randomised treatment order either at baseline or after the last dose of placebo, but in each case just before the first dose of enalapril.

We used Spearman's rank correlation method. A value of $p < 0.05$ was regarded as significant for two tailed tests.

Results

The effects of enalapril on haemodynamic measurements and circulating concentrations of hormones have been reported in detail elsewhere.²⁰ Table 1 summarises the haemodynamic effects of long term treatment. We confirmed that enalapril lowers systemic vascular resistance and blood pressure, and it also lowered pulmonary capillary wedge pressure at rest. Symptoms were significantly improved after treatment for six weeks, although the exercise tolerance was unchanged. Enalapril increased plasma renin activity and reduced aldosterone concentrations, as expected, but did not affect

Table 1 Summary of systemic effects of enalapril during long term treatment

	Baseline		Placebo		Enalapril		Percentage difference	
	Rest	Exercise	Rest	Exercise	Rest	Exercise	Rest	Exercise
Heart rate (beats/min)	83 (15)	114 (22)	88 (14)	128 (34)	94 (20)	124 (26)	+6.3	-2.7
Mean arterial blood pressure (mm Hg)	90 (16)	99 (15)	94 (14)	103 (10)	76 (14)	87 (17)	-19.4*	-15.9*
System vascular resistance (dyne.s.cm ⁻²)	2189 (1003)	1178 (394)	2084 (319)	1177 (388)	1756 (341)	1014 (363)	-15.7*	-13.8
Pulmonary capillary wedge pressure (mm Hg)	11 (8)	19 (13)	13 (11)	19 (9)	9 (7)	16 (10)	-28.3*	-14.6
Cardiac index (l/min/m ²)	2.0 (0.3)	4.0 (1.5)	1.9 (0.2)	4.2 (1.4)	1.9 (0.2)	4.0 (1.2)	-3.6	-6.0

Results are mean (SD). Percentages refer to changes from placebo values during enalapril treatment. * $p < 0.05$, $n = 14$

systemic concentrations of adrenaline or noradrenaline.

Table 2 summarises the short term effects of enalapril on myocardial function. There were no significant changes in coronary sinus blood flow, myocardial oxygen consumption, or catecholamine concentrations in the coronary sinus, either at rest or at peak exercise. There were no short term alterations in the myocardial overflows of adrenaline and noradrenaline by enalapril, but there were very wide variations between patients. Negative values for overflow imply net myocardial uptake.

Six weeks of treatment with enalapril produced no significant change in exercise tolerance. The mean (SD) exercise duration was 578 (282) s, compared with 615 (288) s after six weeks of placebo; both figures were higher than baseline values (538 (282) s), but there were no significant differences between enalapril and placebo values. There was also little change in total body oxygen consumption, which was reduced by 18% at peak exercise (NS) after enalapril compared with placebo. However, heart work was reduced: the double product (systolic blood pressure $\times$ heart rate) was 18.6% lower after enalapril than after placebo at rest ($p < 0.05$) and by 20.6% at peak exercise ($p < 0.05$) (table 3), and the stroke work index at rest was 22% lower after enalapril than after placebo ($p < 0.05$). Myocardial oxygen consumption was also lower after enalapril, by 10.5% at rest

and 25.8% at peak exercise, but these changes were not statistically significant. Coronary sinus blood flow was 5.9% lower at rest and 16.1% lower at peak exercise (both NS); the difference in oxygen content between arterial and coronary sinus blood was 7.2% lower at rest and 12.5% lower at peak exercise (both $p < 0.05$).

Arterial noradrenaline concentrations were unaltered after six weeks' treatment with enalapril but noradrenaline concentrations in the coronary sinus were lower than after placebo by 17.3% at rest (NS) and by 27.1% at peak exercise ($p < 0.05$) (table 3). Myocardial overflow of noradrenaline was 55% lower at rest (NS) and 88% lower at peak exercise ($p < 0.05$). It was also substantially lower after enalapril than at baseline, both at rest and on exercise.

The mean concentration of adrenaline in the coronary sinus and the myocardial overflow of adrenaline were higher at rest after enalapril than at baseline, but myocardial adrenaline metabolism after long term treatment with enalapril was not significantly different from long term treatment with placebo. The negative values sometimes obtained may reflect transmyocardial metabolism of adrenaline or net uptake of adrenaline.

Myocardial oxygen consumption correlated well with double product ($r = +0.62$, $p < 0.001$, for 101 paired observations), and both correlated

Table 2 Comparison between myocardial function (mean (SD)) after short term treatment with enalapril and control data (baseline or placebo) ($n = 9$ unless otherwise indicated)

	Control		Enalapril	
	Rest	Exercise	Rest	Exercise
Coronary sinus blood flow (ml/min)	132.8 (43.8)	183.4 (82.5)	124.5 (61.7)	185.0 (107.0)
Myocardial oxygen consumption (ml/min)	18.1 (5.7)	26.2 (13.0)	26.2 (29.2)	38.5 (35.0)
Coronary sinus noradrenaline (pg/ml)	624 (300)	1199 (467)	628 (231)	1091 (712)
Coronary sinus adrenaline (pg/ml)	543 (621)	805 (743)	609 (715)	705 (823)
Myocardial overflow of adrenaline (ng/min)	-4.7 (24.8)	-14.7 (44.3)	0.9 (16.9)	-0.5 (15.8)
Myocardial overflow of noradrenaline (ng/min)	10.1 (22.6)	17.3 (48.4)	2.4 (19.8)	10.6 (97.8)

Table 3 Effects (mean (SD)) of long term treatment with enalapril and placebo on myocardial function

	Baseline		Enalapril		Placebo	
	Rest	Exercise	Rest	Exercise	Rest	Exercise
Coronary sinus blood flow (ml/min)	118.5 (32.9) n = 8	162.3 (66.8) n = 8	133.3 (39.3) n = 12	201.3 (80.5) n = 12	141.7 (53.0) n = 11	239.8 (116) n = 11
Coronary sinus O ₂ saturation (%)	34.8 (7.4) n = 9	30.4 (9.1) n = 9	33.4 (6.8) n = 11	32.7 (9.6)* n = 12	31.1 (6.5) n = 12	26.4 (6.4)† n = 12
Arterial-coronary sinus O ₂ content difference (ml/dl)	12.8 (2.7) n = 9	14.1 (2.9) n = 9	12.4 (1.4)* n = 11	12.4 (2.4)* n = 12	13.3 (2.0) n = 12	14.2 (2.1) n = 12
Myocardial oxygen consumption (ml/min)	16.2 (5.7) n = 8	24.5 (12.5) n = 8	16.9 (4.9) n = 11	26.1 (12.9) n = 12	18.9 (6.7) n = 11	35.2 (18.7) n = 11
Coronary sinus noradrenaline (pg/ml)	672 (385) n = 8	1117 (567) n = 8	930 (464) n = 11	1491 ((647)* n = 12	1124 (868) n = 12	2044 (1052) n = 12
Coronary sinus adrenaline (pg/ml)	240 (364) n = 8	394 (515) n = 8	888 (896)† n = 11	890 (907) n = 12	492 (544) n = 12	653 (679) n = 12
Myocardial overflow of noradrenaline (ng/min)	19.8 (28.3) n = 8	47.5 (70.4) n = 8	9.0 (66.5)† n = 11	10.6 (105.8)*† n = 12	20.2 (75.1) n = 12	92.5 (133.3) n = 12
Myocardial overflow of adrenaline (ng/min)	-0.8 (50.6) n = 8	-4.7 (25.3) n = 8	17.4 (34.3)† n = 11	26.4 (90.1) n = 12	0.1 (23.6) n = 12	-4.0 (46.7) n = 12
Stroke work index (ml.mm Hg/min ²)	1895 (622) n = 14	2717 (848) n = 14	1412 (454)*† n = 14	2336 (1151) n = 14	1806 (502) n = 14	2844 (1080) n = 14
Double product (mm Hg.min)	10 693 (2364) n = 14	17 427 (5817) n = 14	9799 (2016)* n = 14	16 903 (5722)* n = 14	12 051 (2985) n = 14	21 292 (6576)† n = 14

*p < 0.05 for enalapril v placebo.

†p < 0.05 for enalapril or placebo v baseline.

weakly with myocardial noradrenaline overflow ($\rho = +0.30$, $p < 0.01$, and $\rho = +0.27$, $p < 0.05$, respectively).

Discussion

Patients with chronic heart failure have raised concentrations of noradrenaline in peripheral blood,² reflecting increased sympathetic activity. On exercise, systemic noradrenaline concentrations increase, so that for any given external workload noradrenaline concentrations are higher in patients with heart failure than they are in normal individuals.²¹ Exercise in normal subjects also increases the concentration of noradrenaline in the coronary sinus more than in arterial blood.²² In patients with heart failure noradrenaline release into the coronary sinus is increased at rest, implying abnormally high sympathetic drive to the heart.²³ We showed that with exercise there was a further increase in sympathetic stimulation to failing hearts.

In this study noradrenaline release from myocardial sympathetic neurones was not measured directly, but it was estimated from the calculated myocardial noradrenaline overflow. Previous studies showed that calculated overflow accurately reflects true release²⁴; the assumptions implicit in such calculations (for example that rates of noradrenaline reuptake are constant) are valid except at very much lower flow rates than any in the present study.²⁵ It is also unlikely that the results were influenced by changes in venous haematocrit on exercise. Although

corrections for plasma flow were made by using a single haematocrit measurement taken at rest on each study day, the reduction in plasma volume on exercise is likely to have been as little as 4–7%.^{26,27} Any consequent slight overestimation of catecholamine overflow on exercise would have affected both placebo and treatment data, and it is unlikely that this could have significantly influenced the results. Similarly, any reduction in coronary sinus oxygen saturation due to ischaemia would have affected both placebo and treatment data; however, there was no symptomatic or electrocardiographic evidence of exercise induced ischaemia in any of these patients.

The statistical data from this study were analysed by the methods of Hills and Armitage for a crossover trial.¹⁹ There were significant period effects influencing short term placebo data, and so the short term effects of enalapril (summarised in table 1) were studied with an analysis of variance of data from the first study day only.²⁰ A full Hills-Armitage analysis was hampered by missing data caused by failed coronary sinus catheterisation on some occasions. However, a Hills-Armitage analysis of those variables for which full data were available, showed no period or order effects on long term results. The longer term effects were therefore studied by paired *t* tests. We report in particular the comparisons between long term enalapril and long term placebo data, since this is the most important comparison in a crossover study, once carry over effects have been excluded. The standard deviations of several variables in this study are quite large, because of wide

biological variability and comparatively small numbers of observations, so that although some changes (such as the reduction in peak myocardial oxygen consumption) were not statistically significant they may nevertheless be real and of clinical importance.

The short term effects of captopril, a combination of hydralazine and isosorbide dinitrate,²⁸ and the inotropic vasodilator MDL 17043²⁹ on myocardial catecholamine overflow in congestive heart failure have been studied at rest. Captopril and MDL 17043 did not alter the differences between arterial and coronary sinus noradrenaline concentrations or overflow, but overflow was increased by the hydralazine and isosorbide dinitrate combination. In the present study, enalapril similarly had no short term effect on myocardial noradrenaline overflow, either at rest or on exercise.

We found that myocardial noradrenaline overflow at peak exercise in patients with congestive heart failure was much lower when they had taken enalapril for six weeks than when they had taken placebo. This occurred despite similar levels of exercise, as assessed by duration of exercise or by calculated total maximal oxygen consumption. The reductions in stroke work index at rest and in double product on exercise, together with a substantial (but not statistically significant) fall in calculated myocardial oxygen consumption on exercise, all imply a reduction in myocardial energy requirements on exercise after enalapril. The reduced overflow of noradrenaline may thus be a secondary effect of enalapril, reflecting a reduction in cardiac workload or improvement in cardiac efficiency at any given external workload. Alternatively, it may reflect a direct reduction of the sympathetic drive that is mediated via high concentrations of angiotensin II.^{30,31}

In congestive heart failure the normal increase in heart rate and blood pressure on tilting is blunted, because of decreased tonic inhibition of vasomotor centres by cardiac mechanoreceptors, and because of the impaired ability of the arterial baroreceptors to modulate sympathetic outflow.³² The lack of increase in heart rate in the present study, despite a fall in blood pressure, implies that there may have been some resetting of the baroreceptors. In a previous study with captopril the expected increase in heart rate on tilting did not occur, suggesting a parasympathetic abnormality.³³

The effects reported in this study of enalapril on myocardial function show a mechanism by which angiotensin converting enzyme inhibition may produce a considerable benefit in heart failure. High plasma concentrations of noradrenaline at rest correlate with poor exercise capacity in heart failure³⁴ and with mortality,³⁵ and high levels of sympathetic activity may contribute to potentially dangerous

arrhythmias in this condition.³⁶ A therapeutic reduction in sympathetic drive to the heart may thus be beneficial.

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Restrictive cardiomyopathy and constrictive pericarditis: non-invasive distinction by digitised M mode echocardiography

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SUMMARY It is difficult to distinguish between restrictive cardiomyopathy and constrictive pericarditis on the basis of clinical findings and simple investigation. Cardiac catheterisation has been the reference standard for diagnosis but even this does not always permit an accurate distinction. A Summagraphics digitiser and Prime 750 computer system were used to digitise the echocardiograms of 15 patients with restrictive cardiomyopathy, 10 with constrictive pericarditis and a group of 20 age and sex matched normal subjects of similar age and sex distribution. Compared with controls, patients with restrictive cardiomyopathy showed a significant reduction in the following variables (a) decreased fractional shortening, (b) decreased peak left ventricular filling and emptying rates, (c) decreased percentage posterior wall thickening, and (d) decreased peak left ventricular posterior wall thickening and thinning rates. Whereas patients with constrictive pericarditis only had significantly reduced peak left ventricular filling and posterior wall thinning rates and significantly increased posterior wall thinning rate. When patients with restrictive cardiomyopathy were compared with those with constrictive pericarditis the significant differences were: (a) decreased peak left ventricular emptying rate, (b) decreased percentage posterior wall thickening, and (c) decreased peak left ventricular posterior wall thickening and thinning rates.

Digitisation of M mode echocardiograms, with particular attention to posterior wall function, may be a useful adjunct to cardiac catheterisation in distinguishing restrictive cardiomyopathy from constrictive pericarditis.

Impaired ventricular filling may result from atrioventricular valve stenosis or from reduced "ventricular compliance". The latter may itself be due to disease of the pericardium (constrictive pericarditis), disease of the pericardial space (pericardial tamponade), or disease of the myocardium (for example, restrictive or hypertrophic cardiomyopathy). Pericardial tamponade and hypertrophic cardiomyopathy are readily diagnosed by cross sectional echocardiography but pericardial constriction and restrictive cardiomyopathy giving rise to restrictive pathophysiology are not easily distinguished by echocardiography.^{1,2} Neither do clinical findings or the results of simple investigation always permit such a distinction. Occasionally, even cardiac catheterisation fails to make the diagnosis.³

We describe the features of digitised M mode

echocardiograms that distinguish the restrictive pathophysiology of restrictive cardiomyopathy from that of constrictive pericarditis and which may find clinical application when other diagnostic approaches have failed to distinguish these conditions.

Patients and methods

Between 1973 and 1987 19 908 patients underwent cardiac catheterisation at the Brompton Hospital. From angiographic and haemodynamic data so obtained restrictive cardiomyopathy was diagnosed in 18 patients (eight women and 10 men, age 23-72, mean 67 years) and constrictive pericarditis in 13 (three women and 10 men, age 19-69, mean 64 years). The criteria used at cardiac catheterisation for diagnosis were as follows:

Restrictive cardiomyopathy—Left ventricular angiogram showing predominantly abnormal diastolic function with comparative preservation of systolic function; raised and different left and right

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ventricular end diastolic pressures in the absence of primary valve or congenital heart disease; left ventricular end diastolic pressure usually more raised than right ventricular end diastolic pressure^{4,5};

Constrictive pericarditis—Left ventricular angiogram showing predominantly abnormal diastolic function with comparative preservation of systolic function; equal and raised left and right ventricular end diastolic pressures in the absence of primary valve or congenital heart disease; equal diastolic pressures in all four cardiac chambers; and early diastolic dip and plateau pattern (square root sign) in the ventricular pressure trace.⁵⁻⁷

The case records of these 31 patients were reviewed and the clinical features and results of simple investigations analysed. The symptoms and clinical signs elicited at presentation together with abnormalities documented on the plain posteroanterior chest radiograph and resting scalar electrocardiogram at presentation were noted.

M mode echocardiograms which had been performed in all patients were also analysed to determine whether the two conditions could be distinguished by non-invasive means. Traces were made with Cambridge Instruments equipment with a 2.25 MHz transducer. All patients had been studied in the left semilateral position with simultaneous electrocardiograms and phonocardiograms recorded at a paper speed of 100 mm/s. Records of the left ventricular cavity used for digitisation were taken at the tips of the mitral valve leaflets. Echocardiograms were considered suitable for digitisation if the M mode recording showed clear leading edge endocardial echoes from the septum and posterior left ventricular wall. This condition was satisfied in 10 patients with constrictive pericarditis and 15 patients with restrictive cardiomyopathy. Echocardiograms were digitised by a Summagraphics digitiser and a Prime 750 computer system. At least three cardiac cycles were analysed for each patient and the mean values calculated. The following variables were measured:

- Left ventricular cavity size was measured both at end diastole (EDD (cm)) and end systole (ESD (cm)) (taken as those dimensions synchronous with the Q wave of the electrocardiogram and A₂ on the phonocardiogram respectively).
- Fractional shortening (FS (%)) was derived: $FS = (EDD - ESD) \div EDD$.
- Peak rate of increase of left ventricular dimension during early diastole (LV max rate (cm/s) (this represents peak left ventricular filling rate).
- Peak rate of reduction of left ventricle dimension during systole (LV min rate (cm/s)) (this represents peak left ventricular emptying rate).
- Posterior wall thickness at minimum cavity size

Table 1 *Historical and clinical features*

		Constrictive (%)	Restrictive (%)
Duration of history.	> 1 year	10 (83)	4 (22)
	< 1 year	3 (17)	14 (78)
Presenting symptoms:	Chest pain	0 (0)	4 (22)
	Dyspnoea	13 (100)	14 (76)
Findings on physical examination	Raised venous pressure	13 (100)	18 (100)
	Atrial fibrillation	1 (8)	6 (33)
	Systolic murmur	0 (0)	9 (50)
	S3/S4	3 (23)	7 (39)
Posteroanterior chest radiograph.	Pulmonary venous congestion	0 (0)	9 (50)
	Cardiomegaly	2 (15)	8 (44)
	Pericardial calcification	4 (30)	0 (0)
Scalar electrocardiogram:	ST/T wave changes	9 (69)	9 (50)
	Low voltage QRS complexes	5 (38)	0 (0)

(PW min (cm)).

(f) Posterior wall thickness at maximum cavity size (PW max (cm)) and

(g) percentage systolic thickening of posterior wall (%PW) derived from: $(PW \text{ min} - PW \text{ max}) \div PW \text{ min} \times 100$.

(h) Peak rate of thinning of posterior wall during early diastole (PW max rate (cm/s)).

(i) Peak rate of thickening of posterior wall during systole (PW min rate (cm/s)).

(j) Septal thickness at minimum cavity size (sept min dim (cm));

Table 2 *Haemodynamic data obtained at cardiac catheterisation in patients with restrictive cardiomyopathy*

Patient	LV/RV EDP	RA	PW	CI	Biopsy
1	28/25	—	25	—	F
2	20/14	16	20	—	—
3	22/17	17	35	1.4	—
4	28/10	13	36	—	—
5	28/14	30	30	1.5	HF
6	22/—	16	32	—	F
7	30/20	22	30	1.4	—
8	28/19	10	21	—	—
9	44/32	7	27	—	A
10	45/20	15	40	2.2	—
11	40/28	28	35	—	—
12	36/—	22	33	—	A
13	20/14	12	15	—	A
14	22/23	11	8	—	—
15	21/12	8	22	3.1	—
16	35/28	25	31	1.5	—
17	45/18	5	—	—	—
18	30/20	9	—	—	—
Mean	30/20	16	28	1.8	—

LV/RV EDP, left ventricular/right ventricular end diastolic pressure; RA, right atrial pressure; PAW, wedge pressure; CI, cardiac index; H, hypertrophy; F, fibrosis; A, amyloid. All pressures are mm Hg

Table 3 Haemodynamic data obtained at cardiac catheterisation in patients with constrictive pericarditis

Patient	LV/RV EDP	RA	PW	CI
1	25/25	23	26	2.1
2	13/15	12	12	2.4
3	15/14	14	16	1.9
4	15/15	20	20	1.3
5	17/18	21	25	—
6	23/25	23	23	—
7	20/20	19	—	—
8	17/22	12	22	—
9	19/18	18	19	—
10	28/23	24	23	2.8
11	24/24	20	22	—
12	14/14	12	17	3.6
13	18/18	21	23	—
Mean	18/18	17	18	2.0

LV/RV EDP, left ventricular/right ventricular end diastolic pressure; RA, right atrial pressure; PAW, wedge pressure; CI, cardiac index. All pressures are mm Hg.

(k) septal thickness at maximum cavity size (sept max dim (cm)).

These variables were also measured in a control group of 20 patients of similar age range and sex distribution who had no clinical cardiac disease and a negative stress test at high workload.

Statistical methods

Data are expressed as mean (1 SD). Mean values were compared by Student's *t* test and the relative importance of discriminating variables determined by logistic regression.

Results

Table 1 summarises the clinical features of both groups. Dyspnoea was the major presenting symptom in both groups but the history of this was often shorter in the group with restrictive cardiomyopathy. Physical examination showed raised venous pressure in all patients. Atrial fibrillation occurred in 33% of patients with restrictive cardiomyopathy but in only

8% of patients with constrictive pericarditis. A pansystolic murmur was heard only in patients with restrictive cardiomyopathy but an added diastolic noise was equally common in both groups.

Radiographic evidence of upper lobe blood diversion and left atrial enlargement on the postero-anterior chest radiograph were seen only in patients with restrictive cardiomyopathy; calcification on the lateral chest radiograph seemed to be specific for constrictive pericarditis but occurred in only 30% of such patients. Repolarisation (ST/T wave) changes occurred more commonly in patients with constrictive pericarditis (69% compared with 50% of patients with restrictive cardiomyopathy) while low voltage QRS was found in this group alone but in only 38% of patients.

Tables 2 and 3 show the results at cardiac catheterisation. These data were used to determine diagnosis according to the criteria listed above (see Methods). Those patients with restrictive cardiomyopathy had raised end diastolic pressures in both the right and left ventricles but with a greater increase in the left ventricular end diastolic pressure (left ventricular end diastolic pressure mean 30, range 28–45 mm Hg; right ventricular end diastolic pressure mean 20, range 12–32 mm Hg). Patients with constrictive pericarditis had raised and equal diastolic pressures in all four cardiac chambers. In our series, mean ventricular end diastolic pressure was lower in patients with constrictive pericarditis (mean left ventricular end diastolic pressure 18 mm Hg, mean right ventricular end diastolic pressure 18 mm Hg) than in patients with restrictive cardiomyopathy (mean left ventricular end diastolic pressure 30 mm Hg, mean right ventricular end diastolic pressure 20 mm Hg).

Left ventricular biopsy was performed in 30% of patients with restrictive cardiomyopathy; this confirmed the aetiology in half of them.

DIGITISED M MODE ECHOCARDIOGRAPHY (TABLE 4)

Figure 1 shows typical examples of digitised traces

Table 4 Digitisation of M mode echocardiograms

Variable	Restrictive	<i>p</i>	Constrictive	<i>p</i>	Controls
LV% change	22 (9.8)	< 0.001*	30.5 (10.2)		36 (5.8)
LVmax rate (cm/s)	7.5 (3.3)	< 0.001*	8.8 (2.5)	< 0.004*	12 (2.6)
LVmin rate (cm/s)	-5.3 (1.7)	< 0.001*	-8.5 (2.8)		-8.3 (1.1)
PW%	24% (12)	< 0.006†	47% (15)		35% (7)
PWmax rate (cm/s)	2.6 (0.9)	< 0.007*	6 (2.8)	< 0.01*	3.4 (0.7)
PWmin rate (cm/s)	-4.1 (2.5)	< 0.008†	-6.7 (1.9)		-5.8 (1.8)
		< 0.004†			
		< 0.02*			
		< 0.007†			

*Test of significance against controls

†Test of significance against group with constrictive pericarditis

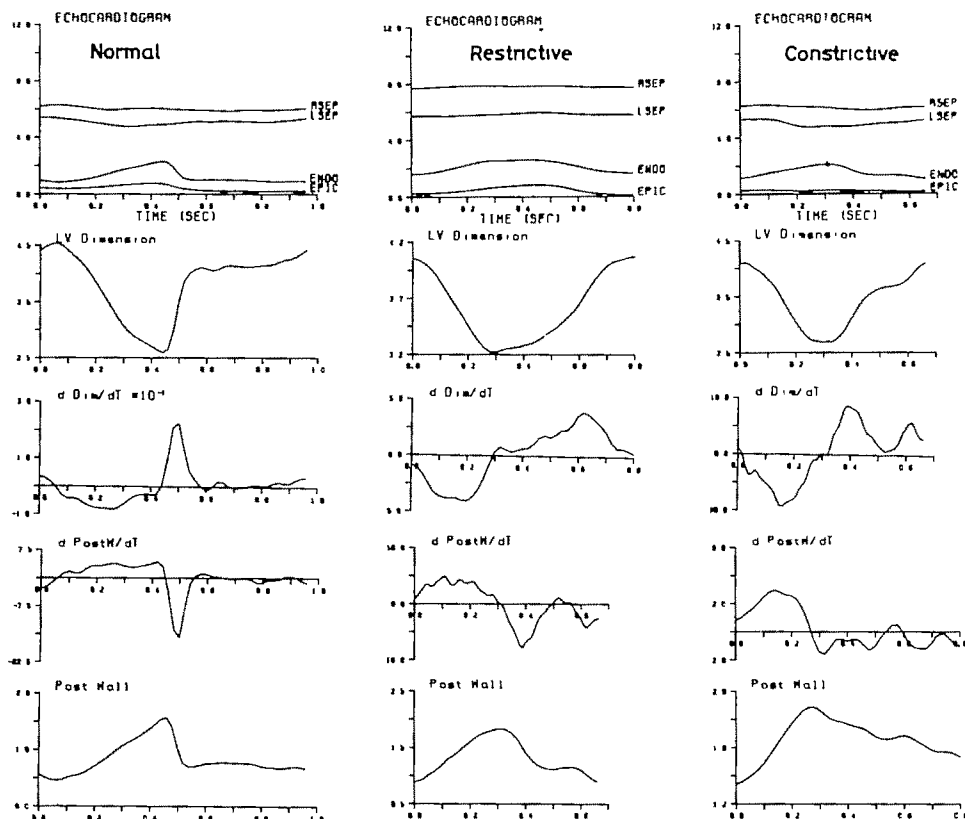


Fig 1 Typical examples of computer printouts of digitised echocardiograms from a control, from a patient with restrictive cardiomyopathy, and from a patient with constrictive pericarditis. R, right; L, left; SEP, septum; ENDO, endocardium; EPIC, epicardium; LV, left ventricle; $d \text{ Dim}/dT \times 10^{-1}$, rate of change in left ventricular dimension; $d \text{ PostW}/dT$, rate of change in thickness of posterior wall.

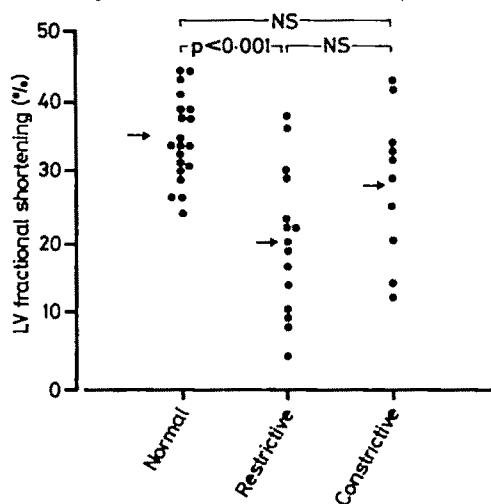


Fig 2 Left ventricular fractional shortening (LV%) (see text) in controls, patients with restrictive cardiomyopathy, and patients with constrictive pericarditis.

obtained from controls, patients with restrictive cardiomyopathy, and patients with constrictive pericarditis.

There was no significant change in left ventricular cavity dimension at end systole or diastole in either restrictive cardiomyopathy or constrictive pericarditis as compared with control patients.

Fractional shortening was significantly less in the group with restrictive cardiomyopathy than in the controls (mean 22 (9.8) % *v* 36 (5.8) %, $p < 0.001$) but compared with the group with constrictive disease the difference did not achieve statistical significance (mean 31 (10.2) % *v* 36 (5.8) %). There was no significant difference in fractional shortening between the groups with restrictive cardiomyopathy and constrictive pericarditis (fig 2). Peak rate of increase of cavity dimension in diastole (LV max rate, that is, peak ventricular filling rate) was significantly lower in both constrictive pericarditis (mean 8.8 (2.5) cm/s, $p < 0.003$) and restrictive cardiomyopathy (mean 7.5 (3.3) cm/s, $p < 0.001$)

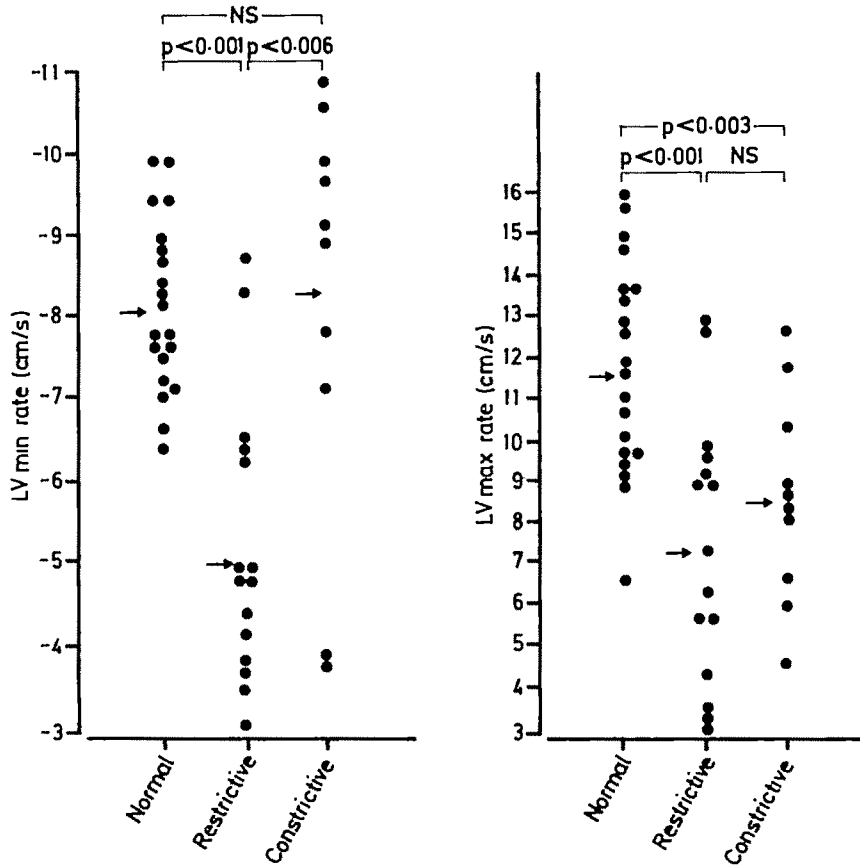


Fig 3 Peak rate of reduction of left ventricular dimension during systole (LV min rate (cm/s)) and peak rate of change of left ventricular dimension during early diastole (LV max rate (cm/s)) (see text) in controls, patients with restrictive cardiomyopathy, and patients with constrictive pericarditis.

than in the controls (fig 3) but this variable was not significantly different in the restrictive cardiomyopathy group and the constrictive pericarditis group. The peak rate of decrease of left ventricular dimension during systole (LV min rate)—that is, peak ventricular emptying rate) for the restrictive cardiomyopathy group (mean -5.31 (1.7) cm/s) was significantly lower than in the controls (mean -8.3 (1.1) cm/s, $p < 0.001$) and those with constrictive pericarditis (mean -8.5 (2.8) cm/s, $p < 0.006$) but the difference between those with constrictive pericarditis and controls was not significant (fig 3).

Posterior wall thickness at minimum cavity size (PW min) and at maximum cavity size (PW max) was not significantly different between the various groups but the percentage posterior wall thickening (% PW) was lower in the group with restrictive cardiomyopathy (mean 24 (12%)) than in either the controls (mean 35 (7%), $p < 0.007$) or the group with

constrictive pericarditis (mean 47 (15%), $p < 0.008$); again the group with constrictive pericarditis did not differ significantly from the controls (fig 4). The peak rate of thinning of the posterior wall during early diastole (PW max rate) was lower in the group with restrictive cardiomyopathy (mean 2.6 (0.9) cm/s) than in either the controls (mean 3.4 (0.7) cm/s, $p < 0.008$) or the group with constrictive pericarditis (6 (2.8) cm/s, $p < 0.004$), in which the rate was significantly faster than in controls ($p < 0.01$) (fig 5). Peak rate of thickening of the posterior wall during systole (PW min rate) cm/s was also lower in the group with restrictive cardiomyopathy (mean -4.1 (2.5) cm/s) than in either the controls (-5.8 (1.8) cm/s, $p < 0.02$) or the group with constrictive pericarditis (-6.7 (1.9) cm/s, $p < 0.007$) but those with constrictive pericarditis were not significantly different from normal (fig 5). It was of interest that the three patients with amyloid disease in the group

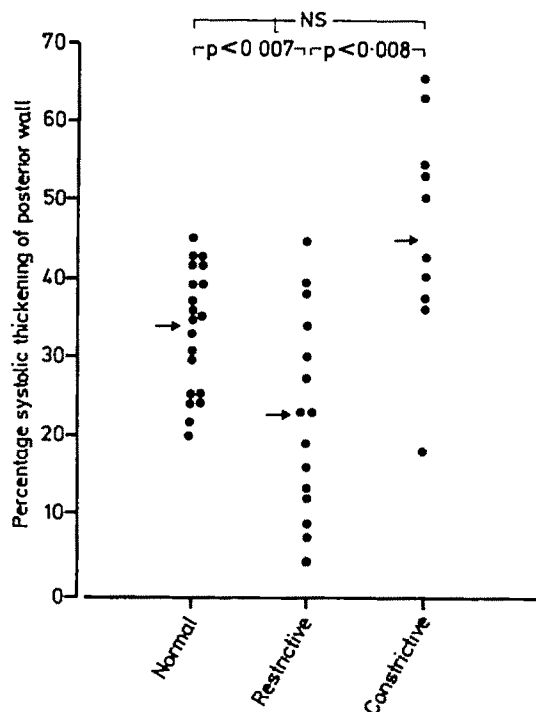


Fig 4 Percentage systolic thickening of posterior wall (see text) in controls, patients with restrictive cardiomyopathy, and patients with constrictive pericarditis.

with restrictive cardiomyopathy were among those patients with the most profound abnormalities of posterior wall variables.

Digitisation of the septum is technically difficult because the leading edge endocardial echoes on the right side of the ventricular septum may be poorly defined. In eight patients, however, this measurement was made and septal dimension during diastole (sept min) was significantly greater in the group with restrictive cardiomyopathy (mean 1.3 (0.5) cm) than in patients with constrictive pericarditis (mean 0.9 (0.4) cm, $p < 0.01$) or controls (mean 0.9 (0.2) cm, $p < 0.01$). However, the maximum septal dimension in both disease groups was not significantly different from control values.

We applied a logistic regression analysis to those variables that were significantly different in restrictive cardiomyopathy and constrictive pericarditis. This showed that peak rate of thinning of the posterior wall during early diastole was the best discriminant. No other variable made a significant contribution once this variable was included. This was because peak rate of thinning of the posterior wall during early diastole was significantly associated with all the other independent variables, in particular peak rate of decrease of left ventricular dimension during early systole, percentage posterior wall thickening, and peak rate of thickening of posterior wall during early systole ($p < 0.001$ for each correlation).

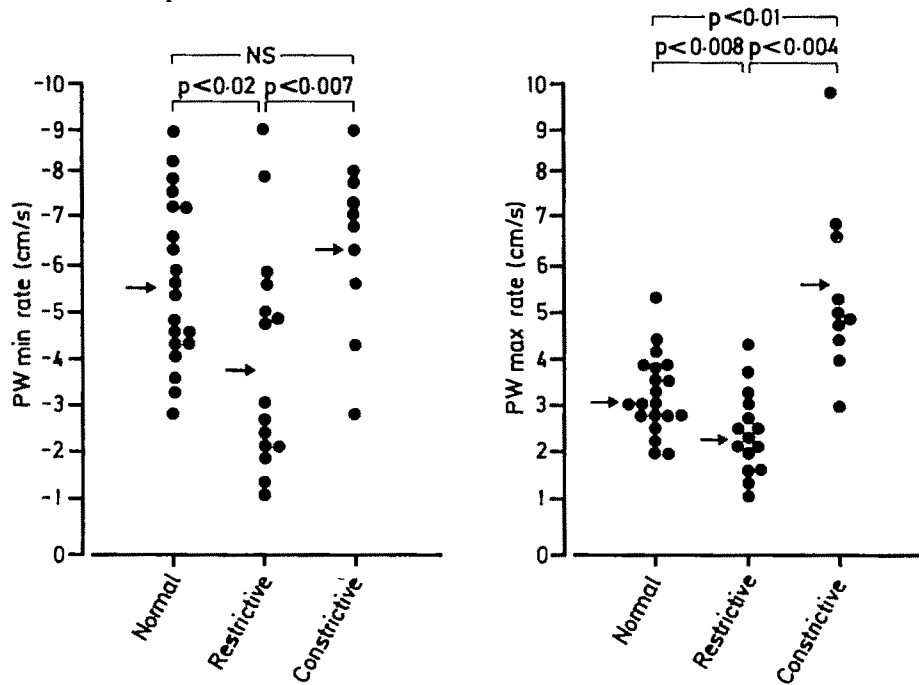


Fig 5 Peak rate of thinning of posterior wall during early diastole (PW max rate) and peak rate of thickening of posterior wall during systole (PW min rate) (see text) in controls, patients with restrictive cardiomyopathy, and patients with constrictive pericarditis.

Discussion

Impairment of ventricular diastolic function with comparative preservation of systolic function is characteristic of restrictive cardiomyopathy⁸ and it is this pre-eminence of diastolic dysfunction that distinguishes this condition from other myocardial disorders in which impaired systolic function is the major abnormality. Constriction of the pericardium, however, also primarily impairs ventricular diastolic function rather than systolic function^{9,10} and hence distinguishing between these two conditions is important, particularly since restrictive cardiomyopathy can only be treated symptomatically whereas the symptoms and signs of pericardial constriction can be dramatically alleviated by pericardectomy.¹¹

Because they have a similar pathophysiology it is not surprising that historical features and findings on physical examination⁹⁻¹¹ do not necessarily permit a clinical distinction. In our series most patients with either restrictive cardiomyopathy or constrictive pericarditis presented with a history of progressive dyspnoea, though those with restrictive cardiomyopathy tended to have had symptoms for a shorter time. Physical signs were also similar in both groups—venous pressure was raised in all patients but atrial fibrillation occurred in only 8% of patients with constrictive pericarditis and 33% of patients with restrictive cardiomyopathy. The murmurs of mitral or tricuspid valve incompetence have been widely reported in restrictive cardiomyopathy,^{10,11} whereas constrictive pericarditis is characteristically associated with a “quiet” heart.³ There are, however, sporadic reports of murmurs caused by atrio-ventricular valve incompetence in constrictive pericarditis.^{9,12} In our series pansystolic murmurs were heard only in patients with restrictive cardiomyopathy. An early diastolic sound may occur in either condition though some would attribute a specific quality to this sound in constrictive pericarditis.¹³ This sound is thought to be caused by sudden deceleration in ventricular filling as a consequence of external restriction. In our series this physical sign was seen in 23% of patients with constrictive pericarditis and 39% of patients with restrictive cardiomyopathy.

Simple investigations may help to establish a diagnosis in some cases. Calcification in the pericardium, best seen on the lateral chest radiograph, is highly specific for constrictive pericarditis but is frequently absent.⁹ We found pericardial calcification in only 27% of patients with constrictive pericarditis and it was never recorded in patients with restrictive cardiomyopathy. Though repolarisation abnormalities (ST/T wave changes) have also

been reported in constrictive pericarditis they are considered to be non-specific and insensitive, and this was our experience.⁹ Though we found low voltage QRS complexes in only the group with constrictive pericarditis they were present in only 33% of patients. It is clear then that clinical observations and simple investigations do not always allow these two conditions to be distinguished.

In our series cardiac catheterisation and echocardiography permitted a diagnosis to be made. At cardiac catheterisation features of the diastolic pressure trace and diastolic pressure measurements have been specifically associated with restrictive cardiomyopathy^{4,5} or constrictive pericarditis^{6,7} (as noted in the methods section). The “dip and plateau” waveform of the diastolic ventricular pressure trace is said to be characteristic of constrictive pericarditis, but not surprisingly it may also occur in restrictive cardiomyopathy since both diseases share a common pathophysiology.^{10,14,15} In certain cases of constrictive pericarditis manoeuvres such as rapid volume infusion at catheterisation may bring out a dip and plateau waveform which is otherwise inapparent.¹⁶ Diastolic equalisation of pressures throughout the cardiac chambers is regarded as a characteristic of constrictive pericarditis but it can also occur in restrictive cardiomyopathy though a difference between left and right ventricular end diastolic pressures; it is more common for left ventricular end diastolic pressures to be higher than right pressure.¹⁷ In one patient in our series (patient 11, table 2) constrictive pericarditis was diagnosed at first cardiac catheterisation and he underwent pericardial resection. It later became apparent that there had been no clinical improvement, and after repeat echocardiography and cardiac catheterisation with endomyocardial biopsy the diagnosis was revised to restrictive cardiomyopathy. Thus if diagnostic uncertainty persists after cardiac catheterisation there may be no alternative but to consider explorative thoractomy³—haemodynamic data do not always lead to diagnosis.

The sensitivity and specificity of endomyocardial biopsy in these groups are undecided.^{18,19} While biopsy was performed in 33% of our patients with restrictive cardiomyopathy it was not performed in any of the patients with the diagnosis of constrictive cardiomyopathy and so we are unable to comment on the value of histological features that may serve to distinguish between the two. It is noteworthy, however, that in one of our cases the diagnosis of amyloidosis rested on the observation of a single island of amyloid deposit in a single section and that it is known that the diffuse nature of amyloidosis makes biopsy diagnosis unreliable.

The M mode and cross sectional echocardi-

graphic features of both conditions have been reported but there is no agreement on the features that distinguish the two groups.^{2,20,21} Pericardial thickness has been considered as a marker for constrictive pericarditis²² but it correlates poorly with the findings at operation, and was not a variable that we have found useful.²³ Janos and colleagues suggested the value of computerised digitisation of M mode echocardiograms in distinguishing between constrictive pericarditis and restrictive cardiomyopathy, but they studied only seven patients.²⁴ Digitised echocardiography has also been used to characterise abnormalities in cardiac amyloidosis.²⁵ Cross sectional echocardiographic features of amyloidosis have been the subject of many reports: myocardial echo intensity and increased thickness of the atrial walls may be moderately sensitive and highly specific.²⁶ Though an increase in myocardial echo intensity is a feature in our patients with amyloidosis there are only three such patients and abnormality of echo amplitude is not a feature in others with restrictive cardiomyopathy. We found no other features on cross sectional echocardiography that enabled us reliably to distinguish the two groups from one another or from the controls.

We showed that there are features on digitisation of M mode echocardiograms that distinguish restrictive cardiomyopathy from constrictive pericarditis and from normal patients. Thus fractional shortening, peak rate of increase of left ventricular dimension during diastole, peak rate of reduction of left ventricular dimension during systole, percentage change in posterior wall dimension, and rate of posterior wall thinning and thickening are all highly significantly lower in the group with restrictive cardiomyopathy group than in the controls. These changes indicate that the group with restrictive cardiomyopathy had slower ventricular filling and emptying (with an associated reduced amplitude of wall motion and rate of posterior wall thinning and thickening) than the controls.

Peak rate of reduction of left ventricular dimension during systole was significantly lower in patients with restrictive cardiomyopathy than in controls—that is ventricular contraction in restrictive cardiomyopathy has a slower peak rate. Also the percentage change of posterior wall dimension is significantly reduced so that in restrictive cardiomyopathy the posterior wall thins and thickens less than in constrictive pericarditis. The peak rate of posterior wall thinning and thickening is significantly slower in restrictive cardiomyopathy than in constrictive pericarditis and indeed posterior wall thinning was significantly faster in the patients with constrictive pericarditis than in the controls. These differences give insight into the abnormalities of left ventricular

function, both systolic and diastolic, that occur in these disease processes. In restrictive cardiomyopathy the myocardium is abnormal with reduced compliance. In constrictive pericarditis myocardium and myocardial compliance are normal, permitting rapid early diastolic filling but this is abruptly terminated by the limit imposed by the constricting pericardium. Digitisation of the M mode echocardiogram may also find a clinical application when other methods have failed to distinguish these two conditions. Analysis by logistic regression suggests that for diagnostic purposes peak rate of thinning of the posterior wall during early diastole is the best discriminant. Distinction between restrictive cardiomyopathy and constrictive pericarditis will not be enhanced by the inclusion of other variables because the peak rate of thinning of the posterior wall during early diastole is significantly associated with all other independent variables and in particular with peak rate of decrease of left ventricular dimension during early systole, percentage posterior wall thickening, and peak rate of thickening of posterior wall during early systole.

The history, physical examination, and simple investigations cannot be used to distinguish between restrictive cardiomyopathy and constrictive pericarditis. A diagnosis can usually be made at cardiac catheterisation by careful pressure recording from the four cardiac chambers (indirectly by means of the pulmonary wedge pressure from the left atrium) but unfortunately there can still be overlaps. If the diagnosis is in doubt, digitisation of M mode echocardiograms, with particular attention to posterior wall function, may improve the distinction between these conditions.

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Electrode catheter ablation for ventricular tachycardia: efficacy of a single cathodal shock*

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SUMMARY Electrode catheter ablation was used to treat 11 distinct types of sustained ventricular tachycardias in eight patients. Rigid electrophysiological criteria were used to identify five left and five right ventricular arrhythmogenic sites; one of them gave rise to tachycardia with two distinct configurations. A single R-wave-synchronised 250 or 150 J cathodal shock was delivered at each site. One patient had mildly symptomatic episodes of sustained ventricular tachycardia during the first four days after the shock—there were no other complications. At discharge none of the patients was taking antiarrhythmic drugs. They were followed for 8–20 months (mean 14). Ablation abolished five of the 11 ventricular tachycardias. There was no recurrence in three of the eight patients. In two patients identical ventricular tachycardias recurred because the identification of the arrhythmogenic site was incorrect.

Ablation of arrhythmogenic sites (origin of tachycardia) by a DC shock given by a catheter electrode is an attractive alternative for the treatment of ventricular tachycardia that is refractory to drugs.¹⁻³ Multiple high energy shocks were used in several clinical studies to enhance the efficacy by disrupting alternative pathways in an extended arrhythmogenic area.^{1,3,4} But death and serious complications were reported and were related to the high energy used.⁵ We evaluated the efficacy of a single cathodal shock to the presumed arrhythmogenic site.

Patients and methods

PATIENTS

We used the following criteria to select appropriate candidates for ablation: (a) presence of spontaneous episodes of symptomatic uniform sustained ventricular tachycardia; (b) refractoriness to or

intolerance to at least three antiarrhythmic drugs; (c) without accepted indications for surgical treatment; (d) only one or two predominant distinct configurations of ventricular tachycardia during spontaneous episodes when the patient was not taking antiarrhythmic drugs; (e) identification of the arrhythmogenic site(s) according to rigid criteria (see below).

ENDOCARDIAL CATHETER MAPPING

Details of endocardial catheter mapping have been described previously.⁶ A new 6F quadripolar USCI catheter (interelectrode distance 0.5 cm) for mapping and shock delivery was introduced into either the femoral artery or vein and advanced to the left or right ventricular cavity. Recording of two bipolar electrograms derived from the distal and proximal pairs of electrodes could be obtained simultaneously with the four unipolar electrograms from these electrodes. Filters were set at 50–1000 Hz for the bipolar recordings and at 0.1–1000 Hz for unipolar recordings. The aortic pressure was monitored during the entire mapping and ablation procedure via the side channel of the arterial introducer.

We tried to identify the arrhythmogenic site of each distinct ventricular tachycardia. Criteria for identifying the configuration are given in a previous article.⁶

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CRITERIA FOR ELECTROPHYSIOLOGICAL IDENTIFICATION OF THE ARRHYTHMOGENIC SITE

We used the following rigid criteria: (a) during extensive activation mapping of ventricular tachycardia the earliest local distinct diastolic potential (index potential) was consistently recorded each consecutive cardiac cycle; (b) the relation of this index potential to the subsequent QRS complex of ventricular tachycardia was constant during spontaneous or pacing induced change of the interval between consecutive index potentials; (c) the index potential was absent during normal sinus rhythm but suddenly appeared before the first QRS complex of a distinct ventricular tachycardia; (d) the index potential suddenly disappeared or changed its configuration after the last QRS complex showing the configuration of ventricular tachycardia.

The second, third, and fourth criterion indicate a causal relation between the index potential and the subsequent QRS complex of the tachycardia. The first criterion and at least one of the other criteria were regarded as essential for the identification of the arrhythmogenic site. If the QRS configuration was identical during ventricular tachycardia and during pacing this was regarded as additional evidence.

ELECTRICAL CATHETER ABLATION

The catheter electrode at the arrhythmogenic site from which the most prominent unipolar index potential was recorded was subsequently connected to a switchbox. This permitted recording to continue or connected the area to the cathodal output of a standard defibrillator (Datascope M/D 2). The characteristics of this device are: Capacity 40 μ F, value of the inductor 36 mH, internal resistance of the inductor 10 Ω . The anodal sink of the defibrillator was connected to a large external chest patch. This patch was positioned under fluoroscopic

control, placing the target tissue between the cathode and anode.

Then the patient was sedated with intravenous etomidate. The defibrillator was charged and during stable recording of the index potential the appropriate catheter electrode was switched to the cathodal output. Immediately afterwards the defibrillator was discharged (sinusoidal 5 ms pulse) synchronously with the QRS complex. Only a single shock was delivered to each arrhythmogenic site. The energy delivered during each shock was approximately 250 J (stored energy 300 J) with the exception of two shocks delivered to the thin right ventricular wall where approximately 150 J (stored energy 200 J) was used. During delivery of the shock the right ventricular apex and the His bundle catheter were left in situ. Afterwards the patients were monitored in the catheterisation laboratory for about one hour. Prophylactic anticoagulant treatment was started and continued for one month. Antiarrhythmic drugs were not used.

TISSUE DAMAGE AND EVALUATION OF HAEMODYNAMIC AND ARRHYTHMOGENIC EFFECTS

The peak concentration of creatine kinase MB isoenzyme was measured by taking blood samples every two hours for up to 12 hours after the shock. The normal value in our laboratory was <5 U/l. Technetium-99 pyrophosphate scans for left ventricular ejection fraction measurements were performed before and two weeks after ablation. Patients were kept in the monitoring area and had continuous two channel Holter recording during the first week after the shock. They performed a treadmill exercise test (Bruce protocol) at the end of the monitoring period and when they were discharged they were not taking any antiarrhythmic drugs.

Table 1 Patients and characteristics of spontaneous ventricular tachycardias

Patient	Age and sex	Structural heart disease	Symptoms during VT	Duration of symptoms (month)	VT episodes in 3 months before ablation (n)	VT cycle length* (ms)	Distinct VT configurations (n)
1	67 M	ASMI	Palpitation, angina	60	6	300	2
2	65 M	ALMI	Dyspnoea	12	28	390	1
3	65 M	ASMI	Palpitation, dizziness	19	3	400	4
4	35 M	RVD	Palpitation, syncopal attacks	140	2	260	2
5	28 F	RVD	Palpitation	120	2	310	2
6	19 F	Corrected VSD	Palpitation, syncopal attacks	23	2	290	2
7	25 F	None	Palpitation, syncopal attacks (exertion)	220	25	200	1
8	53 M	None	Palpitation, syncopal attacks	3	7	260	2

*Mean cycle length of most rapid ventricular tachycardia. ALMI, previous anterolateral myocardial infarction; ASMI, previous anteroapical myocardial infarction; RVD, right ventricular dysplasia; VSD, ventricular septal defect; VT, ventricular tachycardia.

Table 2 Catheter mapping and ablation data

Patient	VT considered for ablation	Presumed site of origin (ablation site)	DA-QRS (ms)	Delivered energy (J)	Catheter electrode used (1 = tip electrode)	CK-MB (U/l)	Efficacy
1	VT ₁	LV antero-septal	75	250	3	42	+
2	VT ₁	LV anterior	130	250	4	7	+
3	VT ₁	LV antero-septal	110	250	4	8	-
4	VT ₁	RVOT septal	35	250	2	38	+
	VT ₂	RV anterior	25	150	1	22	-
5	VT ₁	RV apex	20	150	1	33	+
	VT ₂	RV apex (same site)	5				+
6	VT ₁	RVOT	90	250	1	9	-
7	VT ₁	RVOT anterior*	5*	250	1	30	±
8	VT ₁	LV posterolateral†	5†	250	1	79	-
	VT ₂	LV anterolateral	5	250	1	103	-

CK-MB, peak concentration of creatine kinase MB isoenzyme; DA-QRS, interval between local diastolic activation (index potential) and onset of subsequent QRS complex at presumed site of origin; LV, left ventricle; RV, right ventricle; RVOT, right ventricular outflow tract; VT, ventricular tachycardia.

*Actual site of VT origin was 1.5 cm from ablation site. DA-QRS at actual site of origin was 15 ms.

†Actual site of VT origin was close to ablation site. DA-QRS at actual site of origin was 20 ms.

FOLLOW UP

All patients were followed in the outpatient clinic every month for the first three months and every two or three months afterwards. We paid special attention to recurrences of symptomatic arrhythmias and to late complications.

Results

PATIENTS

Table 1 summarises the clinical characteristics of eight consecutive patients. Sixteen spontaneously (clinical) tachycardias with different configurations were recorded. However, five of these were recorded very rarely and only when the patients were taking antiarrhythmic drugs. The other 11 tachycardia configurations were recorded at least once in patients who were not taking antiarrhythmic drugs. Programmed electrical stimulation initiated 21 patterns of tachycardia, including all 16 tachycardias mentioned in table 1 and five additional non-clinical arrhythmias.

CATHETER MAPPING AND ABLATION

Ten combined mapping and ablation procedures were performed. Six patients had a single procedure and two patients had a second procedure three weeks and three months after the first. Only one single shock was delivered during each procedure.

Table 2 summarises the data on catheter mapping and ablation of tachycardia. Patients never remained in ventricular tachycardia throughout the mapping procedure. Tachycardias were often terminated by catheter positioning. In addition, if a patient became haemodynamically intolerant to the arrhythmia, it was terminated by burst pacing. Each site of origin of

a tachycardia was identified by activation mapping. In addition, six patients had pacing during sinus rhythm at the presumed site of origin. This showed an identical QRS pattern in six of eight tachycardia configurations. A slightly different pattern was recorded during pacing at the site of the two tachycardia configurations in patient 5.

The origin of five tachycardias in four patients was identified at various sites in the left ventricle. Positioning the catheter electrode at posterolateral and anterolateral sites was quite easy, whereas antero-septal and anterior sites of interest could be reached only after extensive manipulation. In these cases a stable position was obtained only after looping the catheter in the apical area and bending its tip upwards. The other six tachycardias originated in the right ventricle—in the outflow tract in three. No particular difficulties were encountered during positioning in the right ventricle.

Extensive mapping showed the earliest local diastolic activation (75–130 ms before the onset of the QRS complex) in patients with a previous myocardial infarction and in the patient with a corrected ventricular septal defect (figs 1, 2, and 3). Diastolic potentials in patients with arrhythmogenic right ventricular dysplasia or with primary electrical heart disease were recorded much later in diastole (5 to 35 ms in front of the QRS complex).

The shock in patient 7 and one of the shocks in patient 8 were later discovered not to have been delivered to the site at which the earliest diastolic potential was recorded. Diastolic activation at that site occurred 10 and 15 ms earlier than at the ablation site (table 2).

Immediately after the shock, appreciable ST segment elevation was recorded in leads II, III, and V1

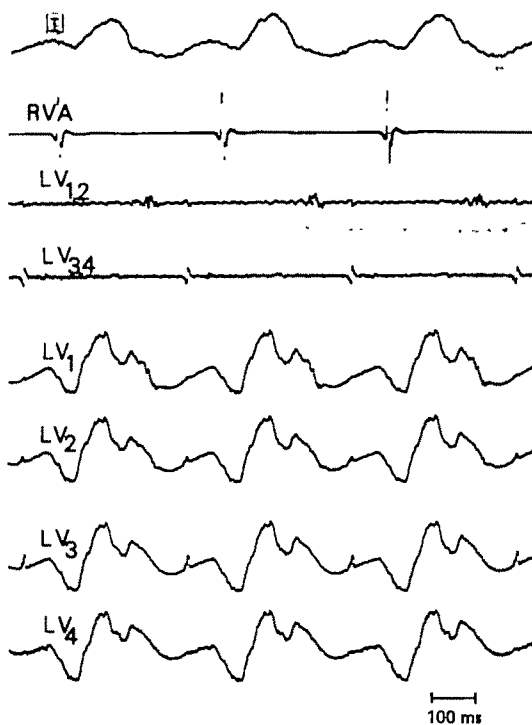


Fig 1 Recordings of a ventricular tachycardia during catheter mapping in patient 1. Figure shows the electrocardiographic lead I, the bipolar right ventricular apex electrogram (RVA), two bipolar electrograms ($LV_{1,2}$ and $LV_{3,4}$) derived from the distal and proximal pairs of electrodes of the left ventricular mapping catheter, and four unipolar electrograms (LV_1 , LV_2 , LV_3 , and LV_4) derived from the left ventricular mapping catheter (LV_1 derived from tip electrode). The most prominent unipolar diastolic potential (index potential) in LV_3 was recorded 85 ms ahead of the RVA reference signal, or 75 ms before the onset of the QRS complex (the onset of QRS in V_1 (not shown here) was 10 ms ahead of the RVA signal). Because a fixed relation between the index potential in LV_3 and the subsequent QRS complex was established by induced cycle change, the third electrode was considered to be positioned at the arrhythmogenic site and was chosen for delivery of a 250 J shock.

in patients 1 and 5. ST segment depression in leads II and III was recorded in patient 7. These changes in ST segment gradually diminished during the next few minutes. Atrioventricular conduction was not disturbed. Systolic aortic pressure was frequently below 90 mm Hg immediately after the shock, but increased to the preshock value within minutes. Patients 7 and 8 felt a burning substernal chest pain after awaking, which responded promptly to intravenous droperidol and fentanyl.

TISSUE DAMAGE AND HAEMODYNAMIC EFFECTS

Serum creatine kinase MB isoenzyme reached its peak value of 37 U/l (range 7 to 103 U/l) two to six hours after the shock (table 2). Table 3 shows the left ventricular ejection fraction measured before and after the last ablation procedure. There was a significant decrease of the ejection fraction in patient 4, who was treated with a shock to the right side of the septum, and in patient 8, in whom two shocks were delivered at different left ventricular sites.

ARRHYTHMOGENIC EFFECTS

Episodes of non-sustained uniform ventricular tachycardia started three minutes after the shock in patient 7 (fig 4). During many recurrences, the QRS configuration was always the same, and identical to that seen before ablation. Extended Holter monitoring after ablation showed the continuation of

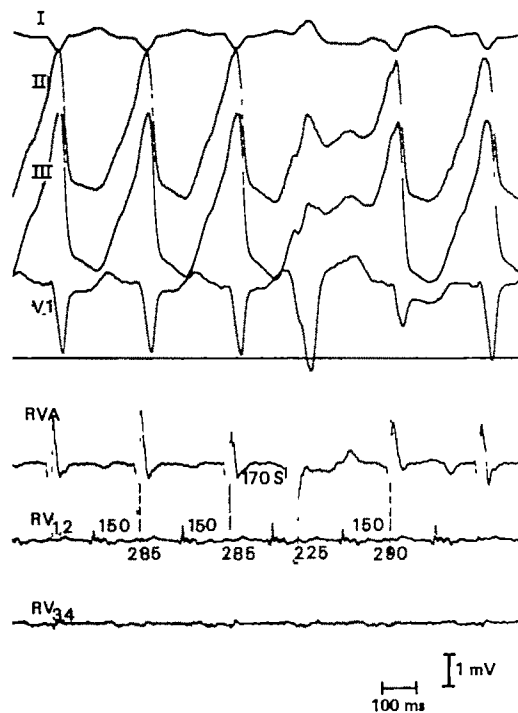


Fig 2 Recordings of a ventricular tachycardia in patient 6 during catheter mapping. The figure shows the electrocardiographic leads I, II, III and V_1 , the bipolar right ventricular apex electrogram (RVA), and two bipolar electrograms ($RV_{1,2}$ and $RV_{3,4}$) derived from the distal and proximal pairs of electrodes of the mapping catheter, which was positioned at the presumed arrhythmogenic site in the right ventricular outflow tract. The index potential in $RV_{1,2}$ was recorded 150 ms ahead of the RVA reference signal, or 90 ms before the onset of the QRS complex, and these intervals remain constant despite the change in cycle length induced by extrastimulus (S).

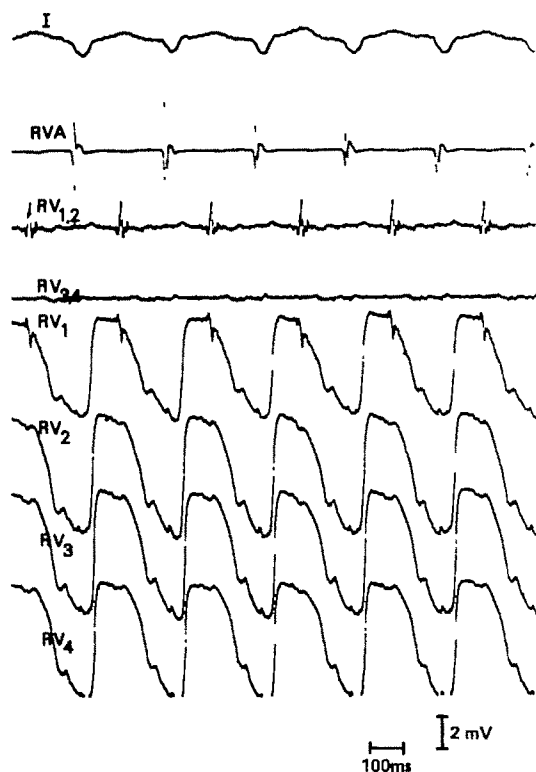


Fig 3 Recordings of the same ventricular tachycardia as shown in fig 2 showing lead I, the bipolar right ventricular apex electrogram (RVA), two bipolar electrograms ($RV_{1,2}$ and $RV_{3,4}$) derived from the distal and proximal pairs of electrodes, and four unipolar electrograms (RV_1 , RV_2 , RV_3 , and RV_4) derived from the electrodes of the mapping catheter (RV_1 derived from the tip electrode). A distinct unipolar diastolic potential was recorded exclusively in RV_1 , suggesting that only the tip electrode was in close contact with the ventricular wall at the site of origin of this ventricular tachycardia. This electrode was used to deliver a 250 J shock. Ablation failed. Compare with fig 1.

numerous episodes of uniform non-sustained and sustained ventricular tachycardia. The average cycle length of these tachycardias was about 400 ms. The minimal cycle length was 340 ms. Figure 5 shows some characteristics of these episodes of tachycardia. Antiarrhythmic drugs were not used because these arrhythmias caused only mild symptoms (palpitation). The frequency of tachycardia rapidly declined on the 4th day. Findings were similar in patient 4; however, the arrhythmias were asymptomatic in this patient.

EFFICACY

Table 2 shows the efficacy of ablation during the

Table 3 Left ventricular ejection fraction before and after ablation

Patient	Ejection fraction	
	Before ablation	After ablation
1	0.15	0.15
2	0.13	0.14
3	0.19	0.18
4	0.50	0.41*
5	0.54	0.56
6	No data	No data
7	0.56	0.56
8	0.50	0.41*

*Measured after second ablation.

follow up period. In patients 1, 2, and 5 there were no occurrences of symptomatic ventricular tachycardia during a follow up of 19, 16, and eight months,

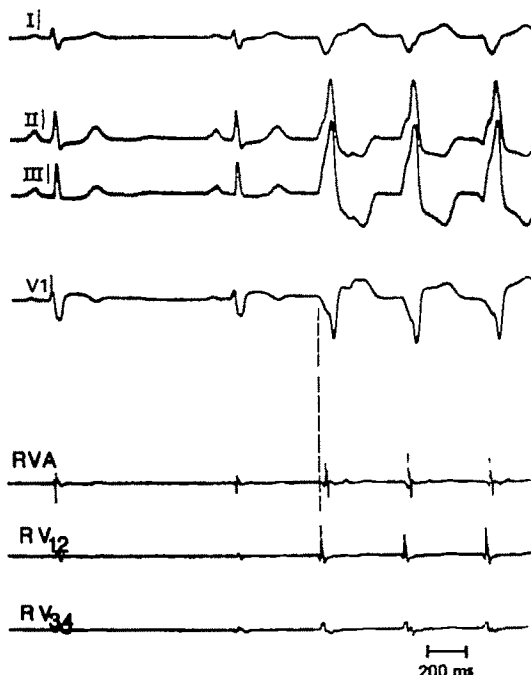


Fig 4 Onset of the first episode of ventricular tachycardia three minutes after a 250 J shock delivered to the arrhythmogenic site in the right ventricular outflow tract in patient 7. The cycle length was 980 ms during sinus rhythm and 440 ms during tachycardia. The coupling interval was 460 ms. The first complex of the tachycardia had the same configuration as succeeding complexes, which was identical with the configuration of the ventricular tachycardia before ablation. The tip electrode of the mapping catheter (used for shock delivery) remained at the ablation site. The bipolar potential derived from the distal pair of electrodes of this catheter coincided with the onset of the surface QRS complex, suggesting that the tachycardia after ablation originated in the vicinity of the site of shock delivery. For abbreviations see fig 2.

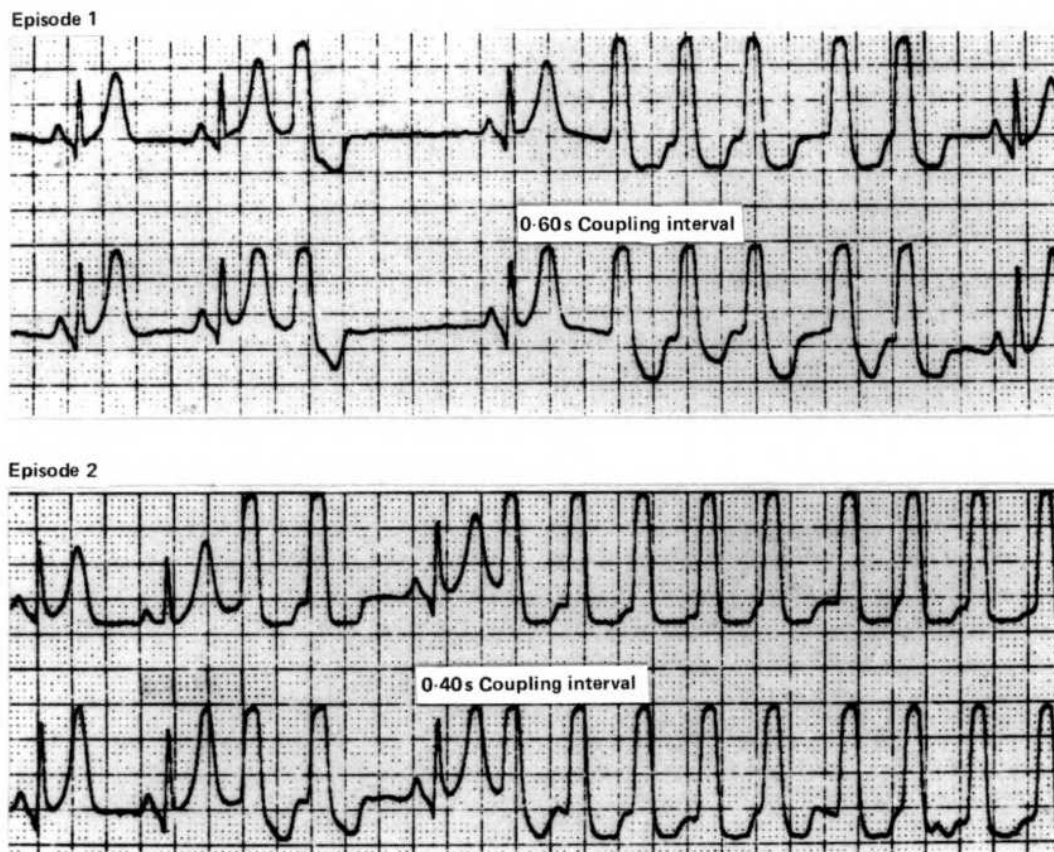


Fig 5 Some characteristics of two episodes of ventricular tachycardia recorded by two channel Holter monitoring in patient 7 after ablation. All tachycardia complexes had the same configuration during each episode. The coupling intervals were 0.60 and 0.40 s, and the cycle length during tachycardia was also variable (0.38–0.50 s). Paper speed 25 mm/s.

respectively. In patient 5 a single 150 J shock successfully terminated two types of tachycardia.

Episodes of ventricular tachycardia before ablation in patient 7 were mostly related to exercise and were associated with many syncopal attacks. The cycle length varied from 270 to 200 ms. Episodes of non-sustained tachycardia with an identical configuration persisted after ablation. These arrhythmias, however, disappeared during exercise and the minimal cycle length increased to 330 ms. Syncopal attacks did not recur. None the less, cryosurgery was performed four months after ablation because frequent recurrences of symptomatic arrhythmias (palpitations) did not respond well to drug treatment.

Symptomatic recurrences with similar configurations and cycle lengths have been documented in the other patients; in two of them additional drug treatment was effective.

Of the 10 configurations of ventricular tachycardia

that were inducible with programmed electrical stimulation but were not considered for ablation, only one recurred during follow up (patient 3).

Discussion

LOW VERSUS HIGH ENERGY

Hypotension, pulmonary oedema, cardiac tamponade, and death have been reported after ablation with DC shock.^{3–5} These complications seem to be related to (a) the size and the number of ablation lesions (local effect) and (b) the height of the pressure wave during the shock (local and remote effects). Both factors are primarily energy dependent.^{7–9} In a previous experimental study a transmural lesion with a volume of 3.2 cc was found one week after a single 250 J cathodal shock.⁷

These observations prompted us to administer one single shock only at each arrhythmogenic site and to

limit the total number of shocks in each patient. In addition, we delivered only 150 J to the thin right ventricular wall in patients with arrhythmogenic right ventricular dysplasia. These restrictions necessitated careful selection of patients and tachycardias considered for ablation and rigid criteria for identification of the arrhythmogenic site.

In patients 7 and 8, who had primary electrical heart disease, we saw dyskinetic transmural ablation lesions with a diameter of about 2 cm at subsequent operation. In patients with pre-existing fibrosis the extent of new damage was less, as demonstrated in patients 2, 3, and 6, in whom the peak creatine kinase MB isoenzyme value was very low (table 2). However, since the arrhythmogenic site in patients with myocardial infarction is usually localised in the border zone, more extensive damage may occur as it did in patient 1 who had a peak creatine kinase MB value of 42 U/l.

Haemodynamic complications did not occur in this study. However, a significant decrease in the left ventricular ejection fraction was seen in two patients.

ARRHYTHMOGENIC EFFECTS

In two patients many episodes of uniform ventricular tachycardia were recorded during the first days after ablation. The course of arrhythmogenicity resembled that seen in experimental ablation in dogs without pre-existing arrhythmias.¹⁰ In addition, the characteristics of postablation tachycardias in patients and dogs were similar (fig 5). For these reasons, we believe that the observed arrhythmias in both patients were caused by the arrhythmogenic effects of catheter ablation. These effects have also been reported by others.^{3,9,11}

EFFICACY

The success rate in our study is similar to the 33% (29 of 88 patients) reported by the Percutaneous Cardiac Mapping and Ablation Registry.¹² However, the mean stored cumulative energy reported to the Registry was 718 J and that used in our study was 280 J.

In our study only one of 10 induced tachycardia configurations for which ablation was not considered recurred. This suggests that these arrhythmias were of limited clinical importance and that we had selected the appropriate tachycardias for ablation. These findings are at variance with those of Tonet *et al* who concluded from their study that all inducible sustained uniform ventricular tachycardias should be ablated.¹³

ANALYSIS OF FAILURES

In patients 7 and 8 there was a definite explanation for the failure of ablation. The shock was delivered at

a site where the diastolic potential was only 5 ms ahead of the QRS complex, and diastolic activity had been recorded (but overlooked) 10 ms and 15 ms earlier at a slightly different site. Conduction velocity may be normal, such as those in these patients who have primary electrical heart disease, so there may have been ≥ 1 cm between the actual site of tachycardia origin and the site at which the shock was delivered. This was confirmed during subsequent operation in patient 7. Intraoperative mapping showed that the actual site of origin was 1.5 cm from the centre of the ablation lesion (fig 6). The site of origin must only have been modified by the shock, and this gave rise to recurrences at a much longer cycle length.

Arcing of current inside the electrode catheter may affect the extent of the ablation lesion and thus the efficacy of ablation.^{14,15} The following signs can be

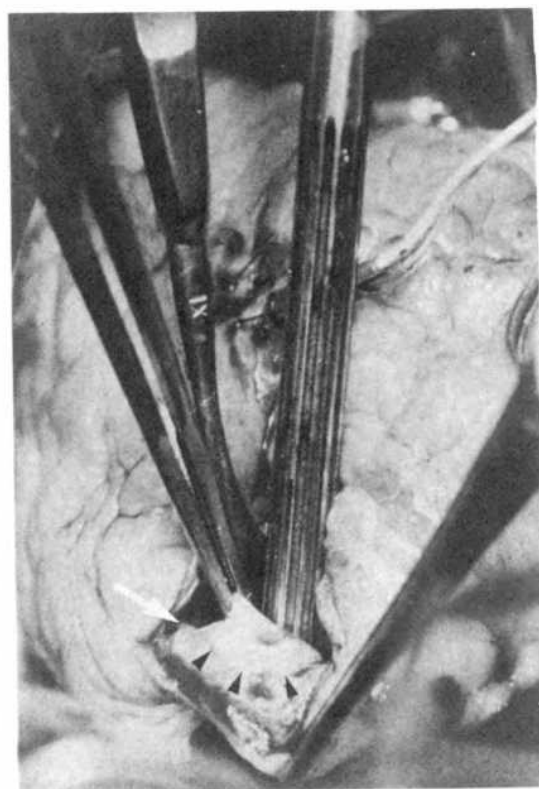


Fig 6 Ablation lesion in patient 7 seen during subsequent operation. An incision was made just apical of a transmural lesion in the anterior wall of the right ventricular outflow tract. The endocardial side of the lesion consisting of white scar tissue (black arrows) is clearly visible. The diameter of the lesion is about 2 cm. Intraoperative mapping localised the origin of the ventricular tachycardia to an endocardial site 1.5 cm from the centre of the ablation lesion (white arrow).

used to assess whether there has been current arcing: (a) recording of two or more identical unipolar electrograms derived from different electrodes, (b) erosion of an electrode other than the one intended to deliver the shock, (c) damage to the insulation of the catheter, and (d) measurement of a change in the resistance. We found none of these signs in our study. It is possible, however, that the contact between the electrode and the ventricular wall may not have been optimal in all cases.¹⁶ Experimental data do not suggest that pre-existing fibrosis forms a barrier to lesion extension.¹⁶

Interpretation of mapping results remains difficult. A causal relation between the index potential and the subsequent QRS complex during tachycardia may be not enough to define the arrhythmogenic site. Alternative pathways are not excluded by this definition. Identification of these pathways and demonstration of a critical relation of the index potential to the next QRS complex may be necessary to enhance the success rate of ablation.

Our results indicate that catheter electrode ablation of the site of origin of ventricular tachycardia by a single cathodal shock, and without additional drug treatment, can be successful provided that the arrhythmogenic site has been correctly identified. We do not believe that all inducible tachycardias of all configurations require ablation. Catheter ablation itself can provoke ventricular tachycardia in the first days after the shock.

Further studies are needed to explain success or failure of electrode catheter ablation.

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Physiological importance of different atrioventricular intervals to improved exercise performance in patients with dual chamber pacemakers

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SUMMARY To determine the importance of different atrioventricular intervals during exercise in patients with dual chamber pacemakers, seven patients with complete heart block and sinus rhythm were exercised in different pacing modes and atrioventricular intervals: (a) ventricular inhibited (VVI) pacing with no synchronous atrial augmentation or rate responsiveness; (b) atrial synchronous ventricular or DDD pacing with a short mean (SD) atrioventricular interval of 66 (4) ms; and (c) DDD pacing with a long atrioventricular interval of 168 (12) ms. Pacing with a short or long atrioventricular interval gave similar maximum heart rates, oxygen uptake at the anaerobic threshold, end tidal pressure of carbon dioxide or oxygen pulse (a measure of stroke volume). Pacing with either a short or long atrioventricular interval produced a significantly higher oxygen consumption and anaerobic threshold and less lactate production than VVI pacing.

During exercise a short atrioventricular interval does not provide a better cardiopulmonary performance than a long atrioventricular interval.

Dual chamber pacemakers that allow synchronous atrioventricular pacing can increase resting cardiac output by as much as 29% compared with ventricular fixed rate pacemakers.¹⁻³ This improvement in exercise capability may be attributed either to an atrioventricular interval that results in a properly timed atrial contraction before ventricular contraction or to the atrial rate responsiveness that permits the ventricular pacing rate to increase with metabolic demands.⁴⁻⁶ It is unclear, however, whether a specific atrioventricular interval will improve haemodynamic function during exercise in patients with dual chamber pacemakers.⁷⁻⁹ This study was designed to measure cardiopulmonary function to determine what atrioventricular interval contributes most to improve exercise performance in patients with dual chamber pacemakers.

Patients and methods

We studied seven patients with dual chamber

pacemakers (table 1). All patients were in sinus rhythm with complete heart block and none had anterograde or retrograde conduction. Patients were able to exercise on a bicycle to exhaustion or leg fatigue. Echocardiograms were performed on all patients.

PACING PROTOCOL

Each patient performed identical exercise testing in two different pacing modes and at two atrioventricular intervals:

Ventricular inhibited pacing (VVI) with the ventricular rate programmed to the sinus rate at rest. Variation in paced rate reflected different sinus rates at rest. This mode meant that there was no synchronised atrial contraction because all patients were in complete heart block and their ventricular rates did not increase with exercise.

Universal or DDD pacing with a short atrioventricular interval as suggested by von Bibra *et al.*¹⁰ The mean atrioventricular interval was set at 66 ms. Patients used their own sinus rate to control the implanted pacemaker. Thus the pacemaker functioned as if it were in the VDD mode during exercise.

Universal or DDD pacing with a long atrioventricular interval of mean (SD) 168 (12) ms. This

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Table 1 Clinical and exercise findings in seven patients with dual chamber pacemakers

Case	Sex	Age (yr)	Weight (kg)	Cardiac diagnosis	Pacemaker	Pacemaker implanted (month)	Short AVI (ms)	Long AVI (ms)	Work rate increments per min (W)
1	M	63	65	IHD	Pacesetter AFP	16	65	165	5
2	M	49	61	None	Pacesetter AFP	7	65	165	10
3	F	60	56	MVR	Pacesetter AFP	2	65	165	5
4	M	62	110	IHD	Cordis Gemini	36	75	175	10
5	M	55	105	IHD	Pacesetter AFP	18	65	165	10
6	M	41	84	AVR	Intermedica Cosmos	13	65	150	15
7	M	24	70	AVR	Pacesetter Genesis	1	65	190	10
Mean (SD)		51(14)	79(22)			13(12)	66(4)	168(12)	11(5)

AVI, atrioventricular interval; AVR, aortic valve replacement; IHD, ischemic heart disease; MVR, mitral valve replacement.

atrioventricular interval was based on previous studies by the authors and others.^{8,9} DDD pacing allowed atrial rate responsiveness in this group of patients with sinus rhythm and resulted in VDD pacing during exercise.

EXERCISE PROTOCOL

All the exercise tests for each patient were usually performed on the same day and there was an interval of at least 30 minutes between tests. Patients were in the preselected pacing mode at least 15 minutes before the start of exercise to allow for equilibration. The different modes for each patient were selected in a random order before exercise. The patient and technician, but not the physicians, were blind to the pacing mode chosen. Informed consent was obtained from each patient and the protocol was approved by the institutional human subjects committee.

Each exercise test consisted of the patient sitting for three minutes at rest, followed by three minutes of unloaded cycling, and then incremental increases in work rate each minute. The work rate was increased by 5, 10, or 15 W each minute and was chosen for each patient to obtain approximately 10 minutes of exercise based on standard tables. Patients underwent maximal exercise on a bicycle until exhaustion or leg fatigue occurred. Because the purpose of this study was to assess the role of atrial augmentation during exercise, the incremental work rate and time

of exercise were kept constant for each individual patient during the three exercise tests. None of the patients was being treated with β blockers or other medications that affected sinus node function. We excluded patients who had <15% increase in sinus rate with exercise (chronotropic incompetence) or more than minimal pulmonary disease by pulmonary function testing. No patients were in heart failure at the time of the study.

EXERCISE EQUIPMENT

The patients exercised on a calibrated, electronically braked stationary cycle ergometer (Godart, Bithoven, Netherlands). They breathed through a rubber mouthpiece attached to a 49 ml deadspace breathing valve (Edward Koegel, San Antonio, TX). The expiratory flow was passed over an ambient-temperature water bath through a Fleisch No. 3 pneumotachograph. A differential pressure transducer (47304A; Hewlett-Packard, Palo Alto, CA) measured pressure across the pneumotachograph to calculate expiratory flow. Gas was sampled at the mouth through a capillary tube at a rate of 60 ml/min and analysed by a mass spectrometer (MGA-1100, Perkin-Elmer, Pomona, CA). Heart rate was continuously monitored and a three lead electrocardiogram was recorded intermittently during exercise to ensure proper pacing.

Table 2 Echocardiographic data in seven patients with dual chamber pacemakers

Case	LVIDd (cm)	LVIDs (cm)	Left Atrium (%)	FS (%)	EPSS (mm)	LVPW (cm)	LVSW (cm)
1	6.0	4.7	3.8	22	CE	1.6	1.6
2	5.0	3.0	2.9	40	10	1.0	1.1
3	3.4	2.0	5.2	41	4	1.0	0.8
4	7.1	5.9	4.5	17	34	1.6	1.0
5	4.4	3.6	4.7	18	14	1.5	1.7
6	4.1	3.0	4.0	29	6	1.6	1.6
7	5.9	3.9	3.7	51	CE	1.0	1.0
Mean (SD)	5.1(1.3)	3.7(0.7)	4.1(0.7)	31(13)	14(12)	1.3(0.3)	1.3(0.4)

CE, cannot estimate; EPSS, E point septal separation; FS, fractional shortening; LVIDd, left ventricular internal dimension at end diastole; LVIDs, left ventricular internal dimension at end systole; LVPW, left ventricular posterior wall; LVSW, left ventricular septal wall.

Table 3 Data (mean (SD)) on cardiopulmonary function in seven patients with dual chamber pacemakers studied during exercise

Exercise variable	VVI	DDD Short AVI	DDD Long AVI	p*
Maximum heart rate (beats/min)	78 (15)	123 (26)	128 (26)	< 0.001
Maximum resp rate (min/l)	33 (8)	36 (7)	33 (8)	NS
End tidal CO ₂ (mm Hg)	34 (7)	37 (8)	36 (6)	< 0.05
Maximum ventilation (l/min)	48.3 (10.5)	46.9 (8.4)	47.0 (8.5)	NS
Maximum oxygen uptake (ml/kg/min)	14.5 (2.7)	15.7 (2.6)	15.6 (2.8)	< 0.05
Respiratory exchange ratio (R)	1.22 (0.15)	1.17 (0.15)	1.17 (0.15)	NS
Anaerobic threshold (min)	8.1 (2.0)	9.8 (2.8)	10.2 (1.6)	< 0.01
Oxygen uptake at anaerobic threshold (l/min)	11.4 (3.9)	13.0 (5.1)	12.8 (4.1)	< 0.025
Oxygen pulse (ml/beat)	16 (10)	11 (6)	11 (5)	< 0.01

DDD, atrial synchronous ventricular pacemaker; max, maximum; VVI, ventricular inhibited pacemaker.

*Statistical significance of difference between VVI and DDD modes. There were no significant differences between DDD modes with short or long atrioventricular intervals (AVI).

EXERCISE VARIABLES MEASURED

Minute ventilation, oxygen uptake, carbon dioxide output, end tidal pressure of oxygen, end tidal pressure of carbon dioxide, and the respiratory exchange ratio were measured every 30 s during rest and exercise. Oxygen pulse, calculated as oxygen uptake divided by heart rate, is an indirect measurement of stroke volume. Maximum oxygen uptake was the highest oxygen uptake measured during the exercise test. Anaerobic threshold was determined by the characteristic gas exchange results associated with the development of lactic acidosis: the point at which the ventilatory equivalent for oxygen ($\dot{V}_E/\dot{V}O_2$) begins to increase while the ven-

tilatory equivalent for carbon dioxide ($\dot{V}_E/\dot{V}CO_2$) remains constant or decreases. The physiological basis and evidence for this relation have been described elsewhere.¹¹

STATISTICAL ANALYSIS

Variables during exercise were compared by an analysis of variance, repeated measures design.¹² All values are expressed as mean (SD). A p value < 0.05 was regarded as significant.

Results

CLINICAL

Three patients had dilated left ventricles and four patients had evidence of reduced left ventricular function as shown by the fractional shortening of the E point to septal separation on the echocardiogram (table 2). There was an increase in left ventricular wall thickness in four patients consistent with left ventricular hypertrophy.

CARDIOPULMONARY FUNCTION

None of the cardiopulmonary indices measured during DDD pacing (that is VDD mode during exercise) were significantly different with short or long atrioventricular intervals (p = NS, table 3). Nor was there any difference in the duration of exercise during short (12.0 (2.2) min) or long (12.5 (1.8) min) atrioventricular intervals or in the VVI mode (11.9 (2.01), p = NS). The maximum work rate was similar with short (61 (36) W) or long (64 (38) W) atrioventricular intervals or VVI pacing (61 (35) W, p = NS).

There were important differences in several cardiopulmonary indices between pacing with short or long atrioventricular intervals and VVI pacing (table 3). As expected, there was a significant difference between maximal heart rate achieved during exercise in patients with VVI pacing and both

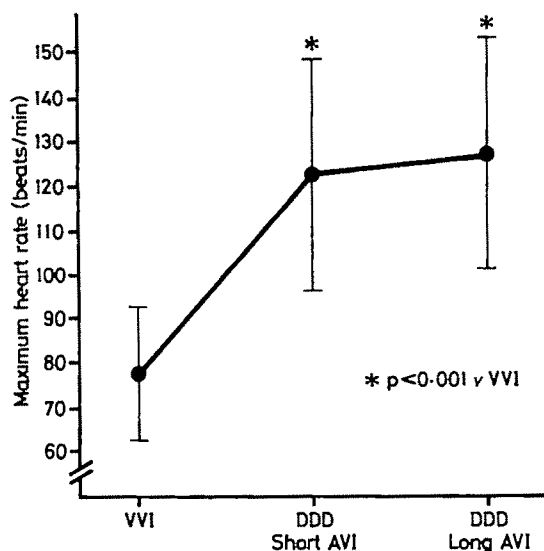


Fig 1 The maximum heart rate achieved during exercise was similar for universal or DDD pacing (that is, VDD mode during exercise) with short or long atrioventricular intervals and was greater than during ventricular inhibited (VVI) pacing. AVI, atrioventricular interval.

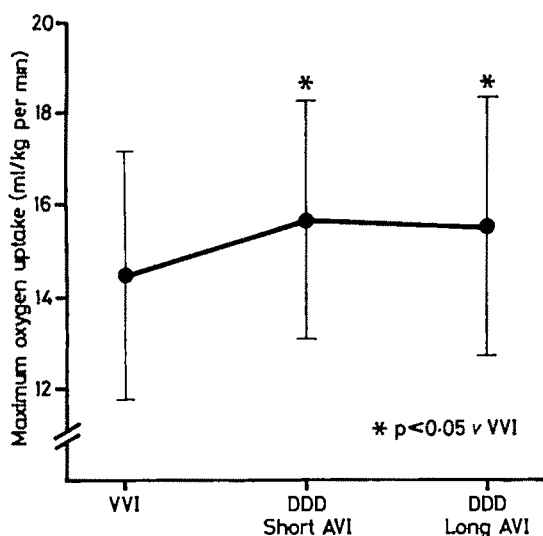


Fig 2 There was no difference in maximum oxygen uptake with either short or long atrioventricular intervals but both settings produced a higher value than ventricular inhibited (VVI) pacing. AVI, atrioventricular interval; DDD, universal pacing.

short or long atrioventricular intervals ($p < 0.001$) (fig 1). The maximum oxygen uptake with short or long atrioventricular intervals was significantly greater than with VVI pacing (fig 2). The end tidal pressure of carbon dioxide with short or long atrioventricular intervals was similar ($p = \text{NS}$), but

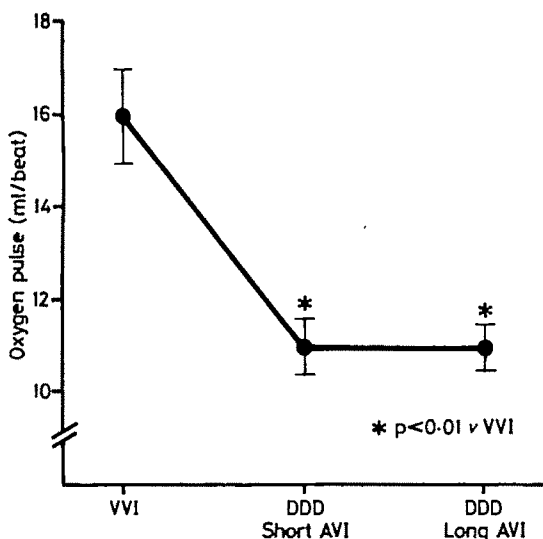


Fig 3 Patients with ventricular inhibited (VVI) pacing attained a higher oxygen pulse than patients with short or long atrioventricular intervals. AVI, atrioventricular interval; DDD, universal pacing.

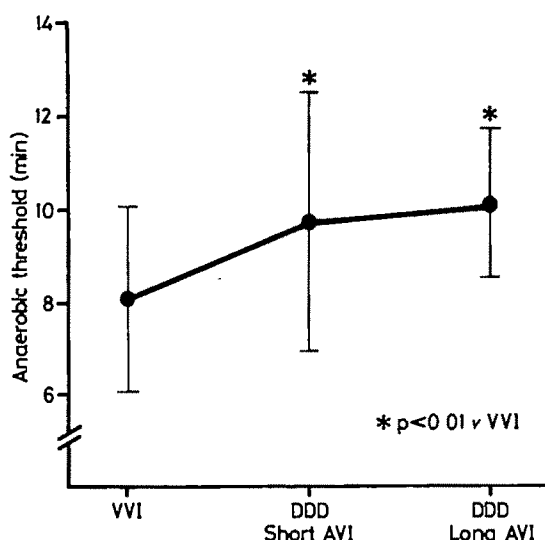


Fig 4 The anaerobic threshold was significantly higher with short or long atrioventricular intervals than with ventricular inhibited (VVI) pacing. AVI, atrioventricular interval; DDD, universal pacing.

both were higher than with VVI pacing ($p < 0.05$). The oxygen pulse (oxygen uptake/heart rate) was higher with VVI pacing than with either short or long atrioventricular intervals ($p < 0.01$, fig 3).

The anaerobic threshold was significantly lower with VVI pacing than with short or long atrioventricular intervals as measured by oxygen uptake at the anaerobic threshold ($p < 0.025$, table 3) or by the time taken to achieve anaerobic threshold ($p < 0.01$, fig 4). Although there were no statistically significant differences among the respiratory exchange ratios for different pacing modes there was a tendency for DDD pacing to give lower values than VVI pacing.

Discussion

In the past decade dual chamber pacemakers have been developed that permit appropriate synchronisation of atrial contraction before ventricular systole. There is little doubt that many patients benefit both clinically and haemodynamically from dual chamber pacing.¹³⁻¹⁵ The correct timing of the atrial contraction in relation to the ventricular contraction is important, because atrial augmentation may increase resting left ventricular end diastolic volume and forward cardiac output in patients with sinus rhythm by as much as 37%.¹⁴⁻¹⁶ However, the usefulness of atrial synchronised contraction at higher heart rates achieved during exercise is unclear.⁶ Universal or DDD pacemakers can optimise the timing of atrial

contraction by varying the atrioventricular interval and exercise performance could be maximised by an ideal setting.

Von Bibra *et al* studied resting M mode echocardiographic measurements in patients with pacemakers and showed that a short atrioventricular interval of 50 ms or 75 ms was likely to promote more physiological conditions by maximising left ventricular filling time.¹⁰ They found that a short atrioventricular interval still produced atrial augmentation of ventricular filling (VDD) probably because of an additional 80 ms electrical mechanical delay between the ventricular pacing spike and the Q wave on the electrocardiogram in patients with pacemakers compared with patients in sinus rhythm. Thus the functional atrioventricular delay was 80 ms longer than the atrioventricular interval set on the pacemaker. They concluded that, theoretically, a setting giving a short atrioventricular interval would be sufficient to maintain normal intervals between atrial and ventricular contraction in paced patients (VDD). However, Haskell and French, using pulsed Doppler derived measurements of cardiac output in resting patients showed that a short atrioventricular interval of 66 ms (mean) gave the lowest cardiac output.⁸

Von Bibra *et al* also showed that a longer atrioventricular interval of 150 ms often meant that the mitral valve closed before the onset of ventricular systole. This would reduce late diastolic ventricular filling and presumably cardiac output. However, others showed that an atrioventricular interval of 150 or 200 ms caused the largest increase in cardiac output but than an atrioventricular interval of 250 ms resulted in a fall in cardiac output.⁸

In the current study there was no significant difference during exercise between a short and long atrioventricular interval, but both settings gave more physiological benefit than fixed rate ventricular pacing. This conclusion is based on measurement of cardiopulmonary function in patients paced in different modes during exercise. Maximum oxygen uptake was higher at both atrioventricular intervals than during VVI pacing, suggesting that both settings gave similar physiological benefits and were better than fixed rate VVI pacing during exercise. Maximum oxygen uptake is probably the best single physiological indicator of a patient's capacity for maintaining heavy work. Factors which limit maximum oxygen uptake are cardiac output, oxygen utilisation by the exercising muscles, and the gas exchange properties of the lungs. Since patients were exercised for the same amount of time and workload, oxygen use by muscles and gas exchange in the lungs were similar in all three paced groups. The increase in cardiac output probably reflected differences in

atrial augmentation or heart rate or both. Values for maximal oxygen uptake were below predicted values for normal subjects because heart function was compromised. But the small changes measured in this group of patients gave an appreciable percentage change in total oxygen uptake during exercise. Most patients in this study had a reduced anaerobic threshold and reduced oxygen uptake at the anaerobic threshold. The mean values for the anaerobic threshold and oxygen uptake at the anaerobic threshold for patients with different atrioventricular intervals were similar and slightly reduced, but both variables were significantly better than in the VVI mode. Since the oxygen uptake at the anaerobic threshold defines the level of work that a patient is capable of sustaining, this suggests that the different atrioventricular settings probably permitted the patient to function at a higher workload, without resorting to anaerobic metabolism, than fixed rate VVI pacing.

End tidal carbon dioxide pressure was higher with both atrioventricular intervals; this was probably because lactate production from muscles was reduced as a result of a higher cardiac output. More lactate was likely produced with VVI pacing because cardiac output was lower. The lactate acidosis stimulates the carotid chemoreceptors and leads to hyperventilation and a lower end tidal carbon dioxide value.

Because the oxygen pulse was greatest with VVI pacing, exercise performance in this mode was probably dependent on increased oxygen extraction by the exercising muscles and not on improved cardiac output from enhanced cardiac function. Since the amount of oxygen that the muscles can extract is limited, this may account in part for the inability of patients to exercise as efficiently in the VVI mode as in either of the other two DDD settings.

ATRIAL AUGMENTATION AND RATE RESPONSIVENESS

This study was not designed to compare the usefulness of atrial synchronised contraction with rate responsiveness. Karlof first showed that only 8% of any improvement in cardiac output could be attributed to atrioventricular synchrony in patients paced during exercise.¹ Fananapazir *et al* found that rate, and not an appropriately timed atrial contraction, was the major physiological determinant of the 40% improvement in exercise performance in patients with rate responsive compared with fixed rate ventricular pacing.¹⁷

Shapland *et al* showed that in dogs with complete heart block synchronous atrial contraction only contributed a small amount to the increase in cardiac output during exercise and that a pacemaker that

increased the rate in response to an increase in metabolic demand maintained haemodynamic values near normal values by exercise.¹⁸

Benditt *et al* and Humen *et al* showed that in patients with an activity initiated, chronotropic-responsive pacemaker the heart was more important during exercise than it was when a single chamber fixed rate ventricular pacemaker was used.^{19,20} Thus it is possible that rate alone, and not a short or long atrioventricular interval, provides the greatest physiological benefit during exercise.

LIMITATIONS OF STUDY

Because this study was not double blind, the exercise time and work rate in exercise periods two and three were subjectively controlled by the physicians to ensure an adequate exercise duration. However, the initial exercise test was performed to a maximal workload. This explains why the duration of exercise and work rate were not different in the different pacing modes. However, other more important variables of cardiopulmonary function, such as oxygen uptake, anaerobic threshold, and end tidal pressure of carbon dioxide are independent of the amount of exercise if anaerobic threshold is reached, as it was in this study.²¹ Also this study related only to the short term benefits of different pacing modes. The long term effects of DDD pacing at different atrioventricular intervals are unknown.

CLINICAL IMPLICATIONS

This study suggests that pacing with short or long atrioventricular intervals is well tolerated and provided similar physiological benefits during exercise in patients with normal or reduced left ventricular function. Clearly, it is not necessary to use unusually short atrioventricular intervals to achieve additional physiological benefits at rest or during exercise. In fact, very short atrioventricular intervals (< 150 ms) may produce unnecessary ventricular pacing and shorten the useful life of the battery.

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Abnormal cardiac signs after Fontan type of operation: indicators of residua and sequelae

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SUMMARY Among 74 survivors of the Fontan type of operation abnormal cardiac signs were detected in 46 (62%) at postoperative examination. The findings were analysed in relation to the state of the cardiovascular system of these patients. Cyanosis was present in 10 (13.5%) patients. The causes of cyanosis included residual interatrial shunt (six patients), acquired pulmonary arteriovenous fistulas (three patients) and acquired systemic-to-pulmonary vein communication (one patient). Signs of chronic fluid retention were detected in six (8%) patients. In four of these the fluid retention was related to conduit obstruction and in the remaining two it was secondary to severe subaortic stenosis in one and atrioventricular valvar regurgitation in the other. Organ heart murmurs were heard in 29 (39%) patients. The aetiologies of these murmurs were multiple. They included aortic valve regurgitation (eight patients), subaortic stenosis (seven patients), atrioventricular valvar regurgitation (five patients), pulmonary valve regurgitation (five patients), residual Blalock-Taussig shunt (two patients), residual ventricular septal defect (two patients), residual communication in the main pulmonary artery which had been ligated but not divided (one patient), and left ventricular to right atrial shunting (one patient). Cardiac rhythm disturbances of varying aetiology were noted in 23 (31.1%) patients. Sixteen (21%) had supraventricular arrhythmias and seven (9.5%) had conduction abnormalities.

The present review suggests that among survivors of the Fontan type of operation abnormal cardiac signs are indicators of residua or sequelae or both of the native cardiovascular anomalies corrected by surgical procedures.

Atriopulmonary or atrioventricular anastomosis of the Fontan type¹ provides long term palliation in some patients with tricuspid atresia and some with complex forms of cyanotic congenital heart disease.²⁻⁴ The best result is a patient without any cyanosis, no fluid retention, and a quiet heart that can maintain an adequate output at rest and during exercise. After a Fontan type operation, abnormal cardiac signs such as cyanosis, chronic fluid retention, an organic heart murmur or arrhythmia cause concern. We studied these abnormal cardiac signs to see what their relation is to the residua and sequelae of the Fontan type of operation.

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Patients and methods

Between January 1976 and June 1986 102 patients had a Fontan or a modified Fontan operation at the Hospital for Sick Children in Toronto. Seventy-four of the 83 survivors were followed for from two months to 8.6 years (mean 2.6 years). Table 1 lists the cardiac diagnoses in these 74 patients who were aged six months to 23.5 years (mean 10.6 years). Sixty-six (89%) had had previous palliative operation to optimise the pulmonary blood flow (table 2). When the Fontan procedure was performed all systemic-to-pulmonary arterial shunts (except the Glenn shunts) were closed surgically. In 34 patients the right atrium to pulmonary artery connection was a direct tissue anastomosis while in six a conduit (three valved and three non-valved) was used. The rudimentary right ventricle was incorporated into the pulmonary circuit.

Table 1 Cardiac anatomy of the 74 patients who had undergone a Fontan operation

		Ventriculo-arterial connection		
		Concordant	Discordant	Double outlet
Present right AV connection (tricuspid atresia)	42	36	6	0
Double inlet ventricle via:	21			
Two AV valves	15	4	9	2
Common AV valve	6	1	2	3
Present left AV connection	2	1	0	1
Others	9	4	4	1
TGA + VSD + straddling MV	2			
TGA + VSD + PS + hypo RV	2			
Cross-cross heart + straddling TV	2			
TOF + hypo RV	1			
AV septal defect + PS + hypo RV	1			
DORV + PS + hypo RV	1			

AV, atrioventricular; DORV, double outlet right ventricle, hypo, hypoplastic, MV, mitral valve; PS, pulmonary stenosis; RV, right ventricle; TGA, transposition of great vessels; TOF, tetralogy of Fallot; TV, tricuspid valve; VSD, ventricular septal defect.

quit in 34 other patients, 12 by direct anastomosis and 2 via a valved conduit. Additional procedures included atrioventricular valve annuloplasty (two patients), arterial switch procedure (three patients), enlargement of a restrictive ventricular septal defect (two patients), and creation of an aortopulmonary window (two patients). We reviewed the in hospital and outpatient records as well as the results of cardiac investigations including cross sectional and pulsed Doppler echocardiography, Holter recordings, preoperative and postoperative cardiac catheterisation and cinecardioangiographic data in these 74 patients. All patients had had at least one echocardiographic examination and 38 (51%) patients had 45 catheterisations in the postoperative period. Abnormal cardiac signs after operation were analysed with reference to the findings at operation and the cardiac investigations before and after operation. The clinical courses of these patients were also noted.

Results

Forty six (62%) patients had one or more abnormal cardiac signs: (a) cyanosis, (b) chronic fluid retention issue oedema, pleural effusions, and ascites), (c) organic heart murmurs, and (d) arrhythmias. Of the

46 patients who had abnormal cardiac signs only 23 were symptomatic (New York Heart Association class II, 12 patients; class III, eight patients; and class IV, three patients). Five of the patients with symptoms died three months to 7.8 years after the Fontan procedure (three at or soon after replacement of the stenotic conduit, one at insertion of a conduit between the left ventricle and descending aorta for severe subaortic stenosis, and one soon after the Glenn shunt was taken down surgically because of cyanosis secondary to pulmonary arteriovenous fistulas).

CYANOSIS

Cyanosis at rest was detected in 10 (13.5%) patients two days to 2.8 years after operation. In nine of them it was noted within 12 weeks of operation. Their systemic arterial P_{aO_2} in room air ranged from 23 to 70 mm Hg (mean 44 mm Hg). The causes of cyanosis included residual interatrial shunts (six patients), acquired pulmonary arteriovenous fistulas (three patients) (fig 1a), and communication between the superior intercostal vein and pulmonary vein (one patient) (fig 1b).

Five of the six patients who had residual interatrial shunts underwent six re-operations two days to 7.8 years after the initial Fontan procedure. The remaining patient who had leakage at the suture line of the atrial patch was treated conservatively because he had severe atrioventricular valvar regurgitation and impaired ventricular function. At re-operation two patients were found to have two residual interatrial communications each and the following types of residual interatrial communications were recognised and repaired: a previously missed congenital communication between the coronary sinus and left atrium (four patients) (fig 1c), a second atrial septal defect that was missed at the initial operation (two patients), and a residual defect at the suture line of

Table 2 Palliative procedures done before the Fontan type II operation in the 74 patients studied

Procedure	No
aval-pulmonary anastomosis:	
Before the Fontan operation	23
At the Fontan operation	9
Waterston's shunt	7
Blalock-Taussig shunt	41
Bott's shunt	9
Pulmonary artery banding	13
Blalock Hanlon septectomy	1
Nil	8

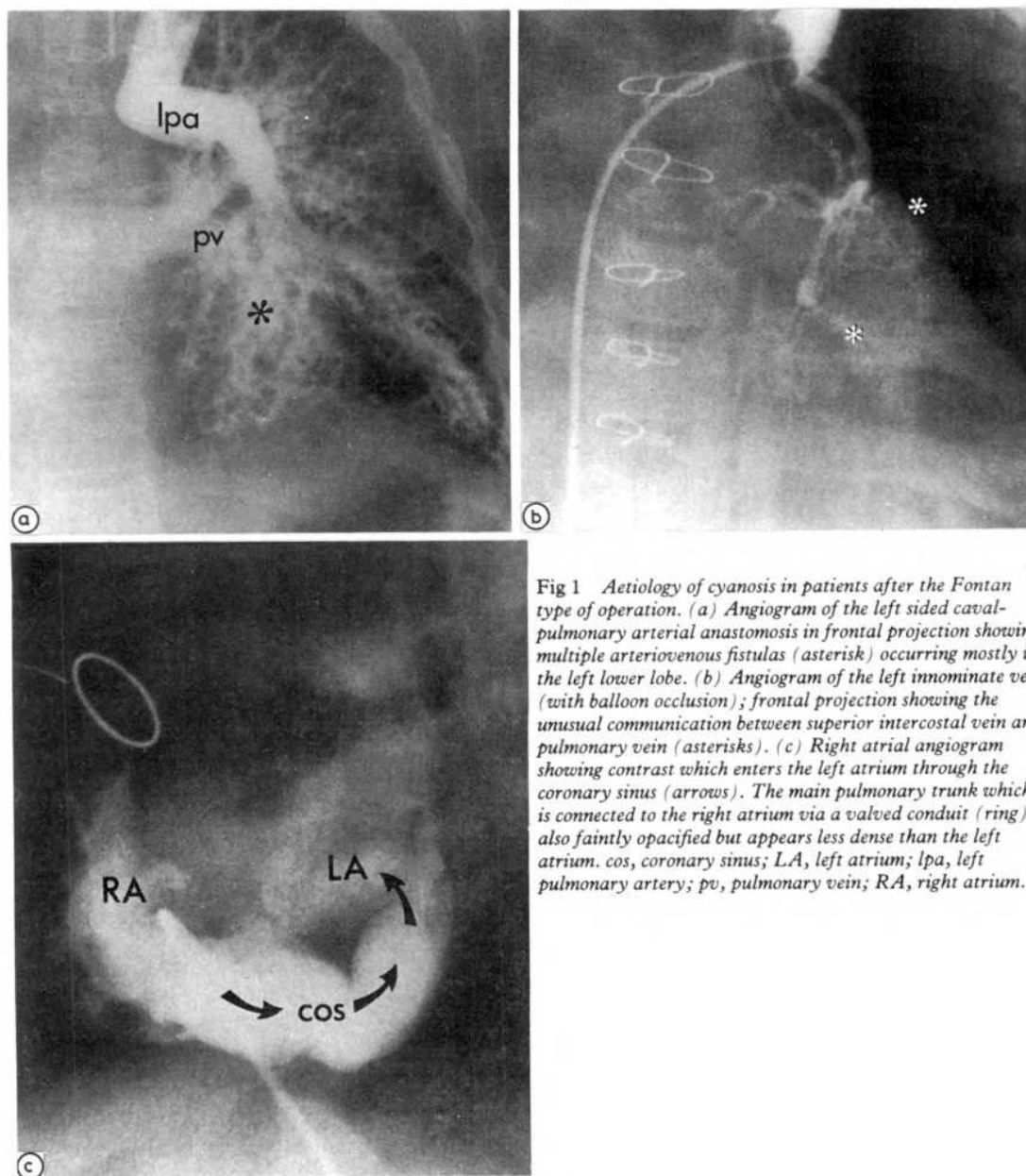


Fig 1 Aetiology of cyanosis in patients after the Fontan type of operation. (a) Angiogram of the left sided caval-pulmonary arterial anastomosis in frontal projection showing multiple arteriovenous fistulas (asterisk) occurring mostly in the left lower lobe. (b) Angiogram of the left innominate vein (with balloon occlusion); frontal projection showing the unusual communication between superior intercostal vein and pulmonary vein (asterisks). (c) Right atrial angiogram showing contrast which enters the left atrium through the coronary sinus (arrows). The main pulmonary trunk which is connected to the right atrium via a valved conduit (ring) also faintly opacified but appears less dense than the left atrium. cos, coronary sinus; LA, left atrium; lpa, left pulmonary artery; pv, pulmonary vein; RA, right atrium.

the atrial septal patch (one patient). All survived the re-operation except the patient who was re-operated for conduit obstruction 7.8 years after the Fontan procedure and in whom closure of residual interatrial communication was incidental.

In three (9.4%) of the 32 patients who had a Glenn shunt pulmonary arteriovenous fistulas developed six to 17.5 years after the shunting procedure (fig 1a).

Two underwent coil embolisation and one became less cyanotic. The third patient died from pulmonary sepsis after the shunt was taken down surgically.

The cyanosis was mild in the patient in whom an unusual communication developed between the superior intercostal vein and the pulmonary vein (fig 1b). However, he became more cyanotic during an episode of supraventricular tachycardia. He was

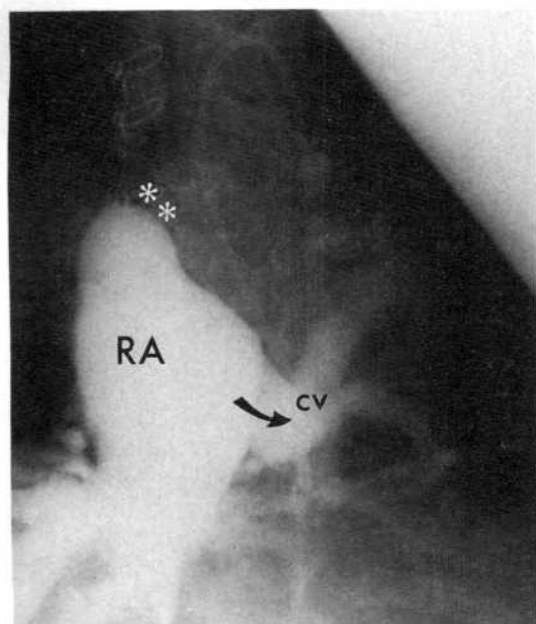


Fig 2 Cause of profound right heart failure in a patient with complete obstruction of the conduit connecting the right atrium to the pulmonary artery. Right atrial angiogram in hepatoclavicular projection showing the absence of forward flow of contrast into the pulmonary trunk (asterisks). There is reflux of contrast into the dilated cardiac veins (arrow) and inferior vena cava. cv, cardiac veins; RA, right atrium.

otherwise well.

CHRONIC FLUID RETENTION

In six (8%) patients persistent oedema, gross hepatomegaly and ascites developed after they had been well for three months to seven years (mean 1.8 years) after the Fontan procedure. In all six patients the mean right atrial pressure was raised (14–27 mm Hg, mean 20 mm Hg) and there was no biochemical evidence of protein losing enteropathy. In four of them there was a coexisting organic heart murmur. The pathogenesis of chronic fluid retention was related to conduit obstruction (fig 2) in four patients (two had an associated mild subaortic stenosis and one had an associated residual interatrial shunt), severe subaortic stenosis (gradient 115 mm Hg) in one other patient, and severe atrioventricular valvar regurgitation in the remaining patient. The last patient was managed conservatively while the other five patients had a repeat operation. Four had conduit replacement, and only one was a long term survivor (one died at re-operation, one each at two months and six months after conduit replacement), and one other patient died at insertion of a valved conduit between the left ventricle and the descending aorta.

ORGANIC HEART MURMURS

Among the 45 patients who did not have an organic heart murmur a soft vibratory functional murmur was heard in 31 (42%) and only 14 (19%) were murmur free. Of the 45 patients 28 (38%) were fully active, without any detectable important residual lesions; eight had arrhythmia; five were cyanotic; one had ascites; three had both arrhythmia and cyanosis; and one had both cyanosis and ascites.

Twenty nine (39%) had one or more organic heart murmurs. We heard 15 long ejection systolic or pansystolic murmurs and 13 early diastolic and three continuous murmurs.

Long ejection systolic (pansystolic) murmur ($n = 15$)

With maximum intensity at parasternal areas—Subaortic stenosis (gradient 10–115 mm Hg) was the underlying cause of the long ejection murmur in seven patients (two had coexisting conduit stenosis, in one other patient there was an associated small shunt from the left ventricle to the right atrium through the surgically “closed” right atrioventricular valve. In three, it was recognised before operation and surgical correction had been attempted. In the remaining four patients it was unmasked after the Fontan procedure (fig 3a). Six of the seven patients had transposition of the great arteries associated with double inlet left ventricle (one with an associated imperforate right atrioventricular valve). The remaining patient had a combination of double inlet and double outlet right ventricle. Only two of these patients had previous pulmonary artery banding. As mentioned above, the three patients with symptoms (two had coexisting conduit obstruction and one had a subaortic gradient of 115 mm Hg) died after re-operation.

A residual ventricular septal defect (Qp:Qs = 1.2:1) was responsible for the pansystolic murmur in two patients with an anastomosis between the right atrium and right ventricle. A residual communication in the main pulmonary artery which had been ligated but not divided was the cause of a high parasternal systolic murmur in one other patient (fig 3b).

With maximum intensity at the apex—An apical pansystolic murmur was heard in five patients with a regurgitant atrioventricular valve (common valve, two patients; left sided valve, two patients; right sided valve, one patient). In four patients the regurgitant valve was discovered after the Fontan procedure. Regurgitation was mild and all four patients remained symptom free. In the fifth patient, despite preoperative recognition and surgical repair, the atrioventricular valvar regurgitation remained severe and the patient was in heart failure.

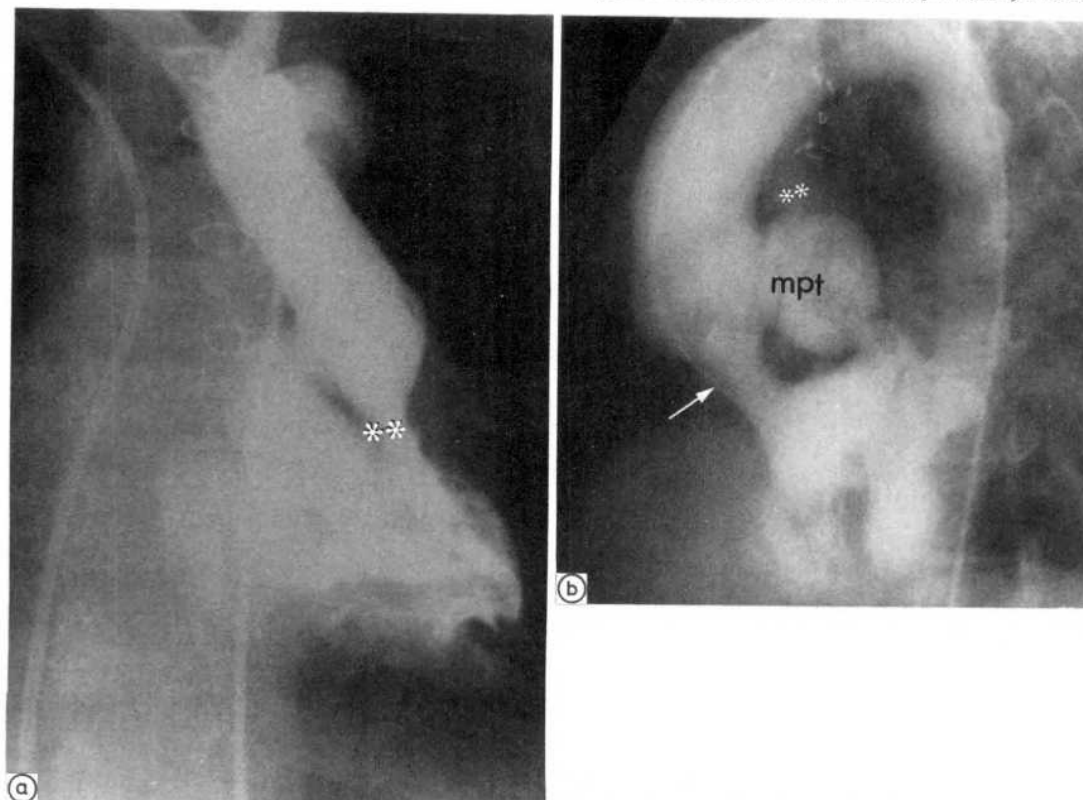


Fig 3 Aetiology of a long systolic or pansystolic murmur in patients after the Fontan type of operation. (a) Left ventriculogram in frontal view showing subaortic stenosis (asterisks) unmasked after Fontan's operation. The patient has transposition of the great arteries associated with a double inlet left ventricle. (b) Left ventriculogram in hepatoclavicular view showing the residual continuity across the surgically ligated (but not divided) main pulmonary trunk (asterisks). The patient has a double outlet right ventricle with mild subaortic narrowing (arrow). mpt, main pulmonary trunk.

Early diastolic murmur ($n = 13$)

Eight patients had a high pitched early diastolic murmur typical of aortic regurgitation: three had a dilated aortic annulus, three had undergone a concomitant arterial switch procedure (fig 4a), one had a congenital quadricuspid aortic valve, and one had coexistent severe subaortic stenosis. In another five patients with a right atrial-right ventricular anastomosis, a low pitched early diastolic murmur was heard indicating pulmonary regurgitation after insertion of a patch across the annulus of the pulmonary valve.

Continuous murmur ($n = 3$)

A continuous murmur was heard over the left chest in two patients who had a small residual left Blalock-Taussig shunt (fig 4b). The latter was successfully closed by catheter embolisation in both patients. The third patient with a continuous murmur was awaiting

further investigation.

ARRHYTHMIAS

Atrial rhythm was disturbed in 16 (21%) patients (six patients had associated atrioventricular valvar regurgitation and one other patient had a coexisting communication between the superior intercostal vein and pulmonary vein). Five had more than one form of atrial arrhythmia and in two patients the rhythm disturbance was present before the Fontan procedure. The atrial arrhythmias were supraventricular tachycardia (six patients), atrial flutter (six patients), junctional rhythm (six patients), and wandering pacemaker (three patients). There were no symptoms attributable to atrial arrhythmias except during an episode of supraventricular tachycardia or atrial flutter when patients experienced palpitation and decreased exercise capacity. The cardiac failure became worse in two patients who were in chronic

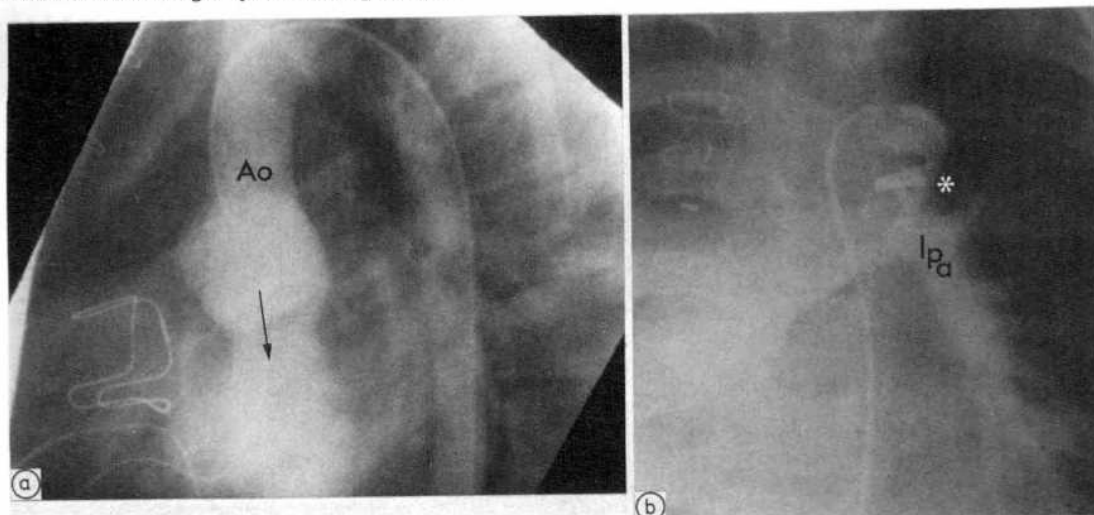


Fig 4 Aetiology of early diastolic and continuous murmurs in patients after the Fontan type of operation. (a) Aortogram in the lateral projection showing moderate aortic regurgitation (arrow) into the main left ventricular chamber. The patient has tricuspid atresia and transposition of great arteries and had undergone an arterial switch operation and modified Fontan's procedure. (b) A left sided Blalock-Taussig shunt persisted after incomplete occlusion by metal clip (asterisk). Ao, aorta; lpa, left pulmonary artery.

heart failure and the cyanosis was increased in the patient who had a coexisting communication between the superior intercostal vein and the pulmonary vein.

Seven (9.5%) patients had complete heart block. In three patients it was present before operation. In the other four patients it was surgically induced during closure of a right sided atrioventricular valve (two patients) or a closure of a large defect in the muscular ventricular septum (one patient) or enlargement of a restrictive ventricular septal defect (one patient). All except one of the patients who were in complete heart block before operation required permanent pacing.

Discussion

We found that most survivors (62%) of the Fontan type of operation had abnormal cardiac signs indicative of residua and sequelae. The commonest abnormal cardiac sign detected was an organic murmur. The pathogenesis of the organic murmur can be deduced readily if the original cardiac anomalies and surgical procedures performed are known. For example, a parasternal pansystolic murmur in a patient who had undergone atrioventricular anastomosis is usually diagnostic of a residual ventricular septal defect. Dysfunctional semilunar and atrioventricular valves and residual systemic to pulmonary artery shunts also have pathognomonic features.

We are surprised that despite a vigilant search

before operation for subaortic stenosis in hearts with a univentricular atrioventricular connection,^{5,6} four patients with this anomaly were not recognised until after the Fontan procedure. In the present study seven (24%) children had organic heart murmurs after operation that were related to subaortic stenosis. When the predisposing anatomy is present, a long systolic murmur after operation may be the first clue to the diagnosis.

The absence of an organic heart murmur, however, does not exclude important residua or sequelae. In our patients, residual interatrial communications and pulmonary arteriovenous fistulas were manifested as cyanosis and important conduit obstruction as chronic fluid retention. The presence of cyanosis after operation precludes long term success and chronic fluid retention is usually also ominous.

Some of the residua and sequelae, such as residual interatrial communications, residual systemic-to-pulmonary artery shunt, and obstruction of the prosthetic conduit are avoidable.⁷⁻¹⁰ But some arrhythmias¹¹ and valve dysfunction³ seem to be inevitable. Further studies to identify these patients at risk and methods to manage these potential lesions are essential if an ideal result is to be achieved in more patients.

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Advantages of colour flow imaging in the diagnosis of left ventricular pseudoaneurysm

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SUMMARY Eleven cases of left ventricular pseudoaneurysm in nine patients were studied by cross sectional echocardiography, conventional Doppler echocardiography, and colour flow imaging. In two patients recurrent pseudoaneurysms developed after cardiac surgery, three had acute rupture after myocardial infarction, two were the result of stab wounds, one was a late rupture of a true left ventricular aneurysm, one developed after surgical resection of a true left ventricular aneurysm, and two as a consequence of left ventricular venting. In all 11 cases the diagnosis was confirmed by angiographic or surgical information or both. The diagnosis was suspected clinically in only four cases. Cross sectional echocardiography alone confirmed the diagnosis in five cases. Neither pulsed wave Doppler nor continuous wave Doppler established the diagnosis when they were used without colour flow imaging in five and three cases respectively. In all 11 cases colour flow imaging showed flow in and out of the pericardial cavity at the defect site as well as the abnormal flow within the pseudoaneurysm. Subsequent use of pulsed Doppler showed a consistent "to and fro" flow pattern across the myocardial defect with characteristic respiratory variation of the peak systolic velocity. This unique intrapericardial flow pattern is diagnostic of a pseudoaneurysm.

Colour flow imaging is a valuable addition to cross sectional and Doppler echocardiography, and is the best technique for detecting left ventricular pseudoaneurysms.

A pseudoaneurysm of the left ventricle is a rare complication of myocardial rupture. Containment of the resulting haematoma by adherent pericardium prevents immediate tamponade and sudden death.^{1,2} Myocardial infarction is the most common cause of myocardial rupture, which can also be a consequence of ventriculotomy and valve replacement (along the valve annulus), penetrating chest injury, and endocarditis.³ The tendency for pseudoaneurysms of the left ventricle to rupture spontaneously has been suggested by pathological studies,^{4,5} whereas true left ventricular aneurysms tend not to rupture. Therefore, the non-invasive recognition of these two types of aneurysm may be useful and relevant to outcome.

Cross sectional echocardiography is helpful in

distinguishing between pseudoaneurysms and true aneurysms of the left ventricle.⁶⁻⁸ However, unless cross sectional echocardiography shows a communication between left ventricle and the pseudoaneurysm sac the diagnosis cannot be confirmed. Pulsed Doppler can show abnormal flow across the myocardial defect into the suspected pseudoaneurysm and thus prove the diagnosis.^{9,10} Colour flow imaging is particularly useful for the diagnosis of abnormal intracardiac shunts because it overlays flow information on the cross sectional image. It should therefore aid the diagnosis of cardiac rupture because it improves the definition of the site of transmyocardial flow.

We studied 11 cases of left ventricular pseudoaneurysm (nine patients) diagnosed by colour flow imaging and we describe the diagnostic features of cross sectional imaging and Doppler echocardiography and the advantages of the colour flow imaging technique over both other ultrasound techniques and left ventricular angiography.

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Patients and methods

PATIENTS

During a two year period we studied nine consecutive patients (from two cardiac centres) with left ventricular pseudoaneurysm by a combination of cross sectional echocardiography, conventional pulsed and continuous wave Doppler, and colour flow imaging. In two of these patients a recurrent or new pseudoaneurysm developed after operative repair. Table 1 shows the cause of pseudoaneurysm and clinical information on the group. There were three cases of acute rupture after myocardial infarction, two after stab wounds to the chest, one case of late rupture of a true left ventricular aneurysm, one case developed after ventriculotomy for resection of a true left ventricular aneurysm, and two cases resulted from left ventricular venting at aortic valve replacement. In the two cases of recurrent pseudoaneurysm, one had a persisting pseudoaneurysm at the same site and the other had a further distal myocardial rupture after cardiac surgery. In the three patients whose pseudoaneurysm followed myocardial infarction, the time from acute infarction to presentation ranged from three months to four years. The patient with rupture of a true left ventricular aneurysm presented 10 years after the preceding infarction. One of the two cases caused by left ventricular venting presented a year after operation. By contrast the two patients with penetrating chest injury presented within 48 hours, and two of the three patients with pseudoaneurysm after cardiac surgery and the two patients with recurrent pseudoaneurysms were all diagnosed within the first postoperative week. The diagnosis was suspected clinically in only four cases and there was a localised precordial systolic/diastolic "to and fro" murmur in three cases. Five cases had clinical and radiographic features of left ventricular failure.

Table 1 Cause of pseudoaneurysm and clinical information on 11 cases

Cause	No	Presentation	Left ventricular failure	Systolic/diastolic murmur
Post infarct	3	Late (3 months-4 yr)	2	2
Chest injury	2	Early (< 48 h)	1	1
Ruptured LV aneurysm	1	Late (10 yr)	1	0
Post cardiac surgery	3 (2)	Early (1-8 days)	1	0
Recurrent pseudoaneurysm	(1) 2	Late (1 yr) Early (3-8 days)	0 0	0 0
Total	11		5	3

LV, left ventricular.

METHODS

Echocardiographic studies were performed by either a Toshiba SSH 65A or a Vingmed 700 colour flow imaging system. Cross sectional echocardiography was performed in the standard parasternal, apical, and subcostal views. When an extracardiac but intrapericardial echo free space that suggested a left ventricular pseudoaneurysm was visualised, an attempt was made to identify any site of myocardial rupture. If a communication between the left ventricle and the echo free space was detected, pulsed and continuous wave Doppler and colour flow imaging studies were concentrated over this area. If no communication was visualised the area of myocardium adjoining the left ventricle and the echo free space were searched for transmyocardial flow—initially by pulsed Doppler and then by continuous wave Doppler and finally by colour flow imaging. Colour flow imaging was performed in the velocity or turbulence mode with appropriate gain and filter settings. If colour flow imaging was successful but conventional Doppler was initially unsuccessful in locating the flow disturbance associated with myocardial rupture conventional Doppler was repeated after realignment through the area of disturbed colour flow to record the Doppler flow pattern.

Results

CROSS SECTIONAL ECHOCARDIOGRAPHY (Table 2) In 10 of the 11 cases we found a significant extramycardial echo free space within the pericardial cavity. The site of this space was posterolateral in seven cases and apical in three cases. This extracardiac echo free space was unequivocally continuous with the left ventricular cavity in only five cases. In a further two cases the site of myocardial rupture was equivocal on imaging and in three cases no

Table 2 Echocardiographic data on 11 cases of pseudoaneurysm

Cause	No	Unequivocal CSE	Diagnostic CW	Diagnostic PW	Diagnostic CFI
Post infarct	3	1	2	2	3
Chest injury	2	1	1	0	2
Rupture LV aneurysm	1	1	1	1	1
Post cardiac surgery	3	2	2	2	3
Recurrent pseudoaneurysm	2	0	2	1	2
Total	11	5	8	6	11

CSE, cross sectional echocardiography, CW, continuous wave Doppler; PW, pulsed wave Doppler, CFI, colour flow imaging; LV, left ventricular.

communication with the extra-myocardial echo free space could be visualised. In the remaining case the pseudoaneurysm cavity was not imaged at the initial study because it was in a very posterolateral position within the pericardial cavity. The pseudoaneurysm was noted only on subsequent colour flow studies when disturbed flow was seen within the posterolateral myocardium, and when the transducer angulation was changed the flow was seen to enter a posterolateral pseudoaneurysm.

Because most pseudoaneurysms occurred in a posterolateral position, subcostal views were obtained in all cases—because in theory this view might increase the diagnostic accuracy of the technique. However, it was not of any additional diagnostic benefit. The presence of thrombus within the pseudoaneurysm cavity was noted in only six cases, occurring in four of the five pseudoaneurysms that presented late and in only two of the six pseudoaneurysms that presented early.

PULSED AND CONTINUOUS WAVE DOPPLER

By identifying the diagnostic transmyocardial flow pattern, both pulsed and continuous wave Doppler confirmed the diagnosis in the five cases with unequivocal cross sectional images. In the remaining six cases continuous wave Doppler made the diagnosis in three whereas pulsed Doppler made the diagnosis in only one of these three cases. In the three (27%) remaining cases cross sectional imaging and conventional Doppler did not establish the diagnosis. After colour flow imaging had localised the myocardial defect, realignment of continuous wave Doppler confirmed the diagnostic flow pattern in all 11 cases whereas pulsed Doppler still failed to show clear diagnostic waveforms in two cases.

The characteristic waveform obtained by both pulsed and continuous wave Doppler consistently showed a multiphasic "to and fro" flow pattern (fig 1). In this example flow into the pseudoaneurysm had two major peaks—the first peak corresponded with

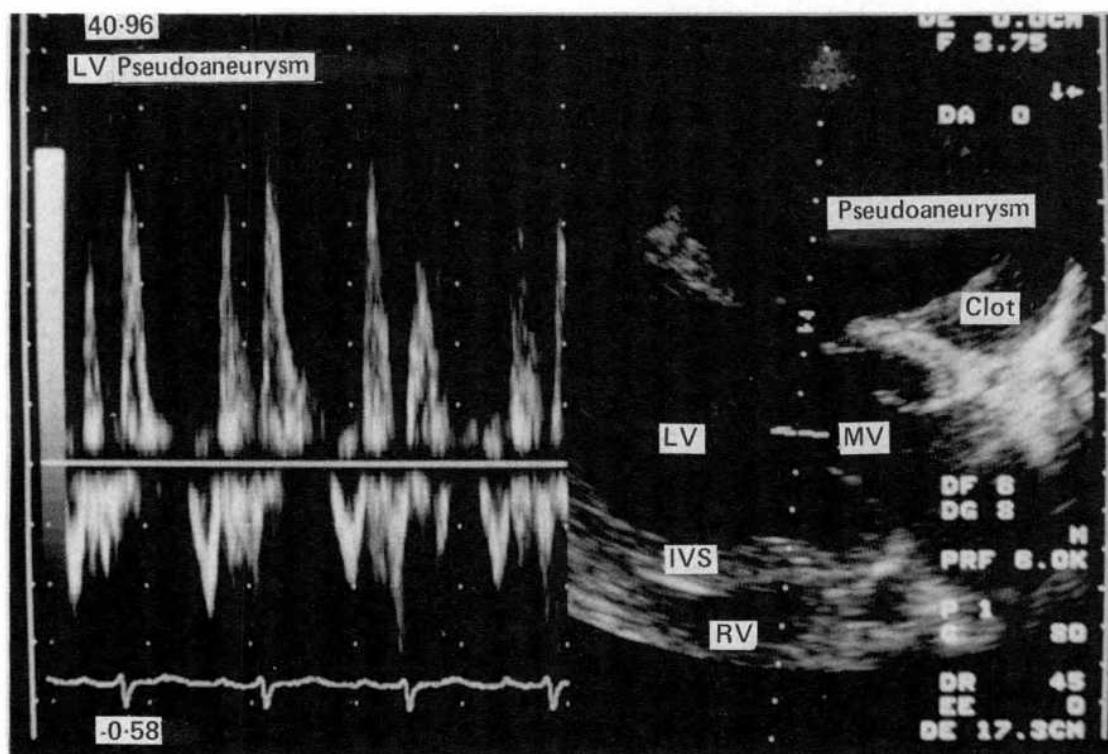


Fig 1 Pulsed Doppler recording from a patient with a left ventricular pseudoaneurysm. The cross sectional image was recorded in a modified four chamber view from a mid-axillary position. The cardiac chambers are displaced by a large posterolateral pseudoaneurysm. The pulsed Doppler sample volume has been positioned at the break in the myocardium. The resulting pulsed Doppler waveform is recorded on the left. Velocities above the zero line indicate flow into the pseudoaneurysm. See text for description of the waveform. LV, left ventricle; MV, mitral valve; IVS, interventricular septum; RV, right ventricle.

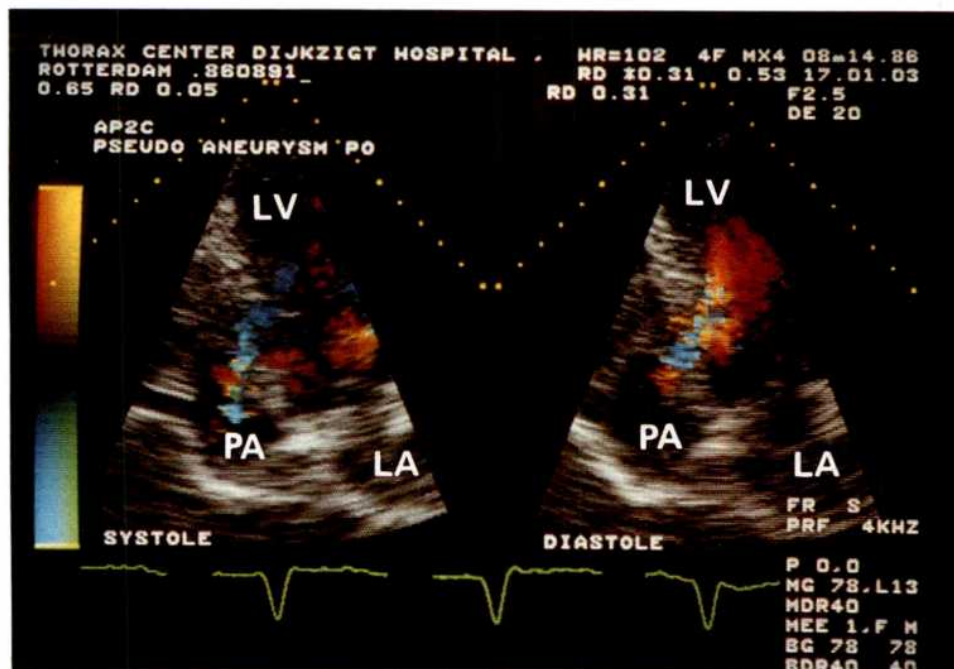


Fig 2 Systolic and diastolic colour flow images (apical long axis view) from a patient with a left ventricular pseudoaneurysm after myocardial infarction (see text). LV, left ventricle; LA, left atrium; PA, pseudoaneurysm.

atrial contraction and the second peak with ventricular systole. Flow out of the pseudoaneurysm started in late systole. The maximum velocity peak in this direction was in early to mid diastole. There was a consistent and often pronounced variation in maximal velocity throughout the respiratory cycle, with inspiration increasing the maximal jet velocity by up to 1.5 m/s. The waveform had a similar configuration to that of the mitral inflow velocities but differed fundamentally in its timing. This flow pattern was characteristic of all 11 cases of pseudoaneurysm studied; it varied only in the peak velocity of the waveforms (that is, the degree of restriction of the myocardial defect) and their degree of respiratory variation in peak velocity.

DOPPLER COLOUR FLOW IMAGING

In all 11 cases of left ventricular pseudoaneurysm colour flow imaging demonstrated one or more systolic turbulent jets exiting from the left ventricular cavity through the left ventricular free wall or apex into an echo free cavity bounded by pericardium. Diastolic turbulence was consistently noted within the left ventricular cavity at the site of the defect. Figure 2 shows a colour flow image of a narrow, turbulent, mosaic jet entering and leaving a posterolateral pseudoaneurysm through a break in

the lateral wall of the left ventricle. In systole a mosaic pattern was identified within the pseudoaneurysm—confirming turbulent flow entering the pseudoaneurysm. In diastole the mosaic pattern occurred within the left ventricle—confirming turbulent flow exiting from the pseudoaneurysm. The extension of the jet and the degree of turbulence varied with respiration. In one patient two jets were found. In early systole they were directed into the pseudoaneurysm and in early diastole they were directed from the pseudoaneurysm into the left ventricular cavity. The diagnosis of all 11 cases was confirmed by left ventricular angiography or operation or both. During the two year study period there were no false positive diagnoses of left ventricular pseudoaneurysm in more than 9000 routine and emergency cases studied in the two echocardiographic laboratories.

Discussion

A pseudoaneurysm of the left ventricle is defined as a myocardial rupture contained by pericardium and thrombus with no remnants of myocardial tissue.^{1,2} It is a rare complication of myocardial infarction, but has also been reported after cardiac surgery, chest trauma, and endocarditis.³ A pseudoaneurysm after

rupture of a true left ventricular aneurysm is rare, although it has been reported as a coincidental finding.¹¹ Clinically and radiographically it is difficult to distinguish a pseudoaneurysm from a true aneurysm of the left ventricle—until recently this required left ventricular angiography. The suggested tendency for pseudoaneurysms to rupture⁴ means that non-invasive recognition of these two types of aneurysm is important because their management may differ, especially in symptom free patients. Cross sectional echocardiography is a useful non-invasive technique for the diagnosis of left ventricular pseudoaneurysms, as is radionuclide imaging,¹² which is not so widely available.

The main echocardiographic features of a left ventricular pseudoaneurysm include: (a) a saccular echo free space outside the perimeter of the left ventricle, which usually contains thrombus; (b) a sharp break in the myocardial echo; and (c) an entry orifice with a diameter that is small compared with the diameter of the pseudoaneurysm cavity. This contrasts with true left ventricular aneurysms where the diameters of the orifice and cavity are approximately equal.^{6,7} However, cross sectional echocardiography may fail to identify small myocardial rupture sites. The differential diagnosis is then a pseudoaneurysm, a localised pericardial effusion or haematoma, and a pericardial cyst or diverticulum. In theory the improved image resolution obtained by transoesophageal echocardiography might improve the identification of small ruptures of the myocardium not visualised by conventional echocardiography. Experience with transoesophageal studies of left ventricular pseudoaneurysms is limited. In two cases in our series transoesophageal echocardiography was performed with the patient anaesthetised before cardiopulmonary bypass. Both were cases of posterolateral pseudoaneurysm and the rupture sites could not be directly visualised in either case. This may reflect the inherent difficulty in imaging the posterolateral and apical aspects of the left ventricle by the transoesophageal approach. Further experience is required before a more definitive statement can be made about any benefits which might be gained by using this new technique in the diagnosis of left ventricular pseudoaneurysm.

The addition of pulsed Doppler has proved a helpful adjunct to cross sectional echocardiography because it increases diagnostic specificity and sensitivity.^{9,10} Pulsed Doppler confirms abnormal flow between the left ventricle and the echo free space at the site of myocardial disruption, thus distinguishing it from echo "drop-out" and can confirm the diagnosis even when the site of myocardial rupture is not visualised. However, in our study the combination of cross sectional and Doppler echocardiography failed

to establish the diagnosis in 27% of cases. In contrast, colour flow imaging showed the communication between the left ventricle and the pseudoaneurysm in all 11 cases. The resultant turbulent jet was used to delimit the area in which continuous wave and pulsed Doppler studies could confirm the characteristic waveform. In addition, colour flow imaging provided information on the flow characteristics of blood within the pseudoaneurysm. Flow was directed along one wall of the pseudoaneurysm towards its most distal point where it turned and then returned along the other wall. The area of disturbed flow was usually restricted to the area around the entry/exit point of the pseudoaneurysm; flow was laminar around the edges.

Echocardiography often shows thrombus within the pseudoaneurysm cavity.⁶⁻⁸ We found thrombus in half the patients we studied; it seemed to be more common in patients with chronic pseudoaneurysms than in those with acute ones.

In nine cases we were able to compare the results of non-invasive tests with those obtained at cardiac catheterisation. In seven cases left ventricular angiography produced good opacification and delineation of the pseudoaneurysm cavity with identification of the "neck" of the pseudoaneurysm. In the other two cases opacification and identification of the "neck" of the pseudoaneurysms were not possible because of dilution of contrast within their large cavities. In these cases the diagnosis was confirmed only by the appearance of the faintest trace of contrast outside the left ventricular contour. Others have also reported that some left ventricular angiograms are unsatisfactory for the diagnosis of left ventricular pseudoaneurysm.⁶

We conclude that colour flow imaging is a sensitive diagnostic technique that should be in addition to cross sectional imaging and conventional Doppler echocardiography for the diagnosis of left ventricular pseudoaneurysm. Cardiac catheterisation can then be reserved for those patients who require precise coronary artery definition before surgical repair.

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Case report

Balloon dilatation of a stenosed bioprosthesis in the tricuspid valve position

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SUMMARY Percutaneous balloon dilatation of a stenosed Ionescu-Shiley bioprosthesis in the tricuspid valve position was performed twice in a 19 year old woman. On each occasion there was a considerable improvement in symptoms and haemodynamic function but the effect lasted for only a few months. When the valve was excised it showed no evidence of the previous balloon dilatations.

Case report

A 19 year old woman presented with a four month history of peripheral oedema, abdominal distension, breathlessness on exertion, and increasing lethargy. Her symptoms had progressed despite diuretic treatment. Soon after birth she had been found to have a ventricular septal defect with pulmonary valve stenosis. When she was six infective endocarditis developed on the tricuspid valve and this produced severe regurgitation. At operation the tricuspid valve was replaced with a 19 mm Björk-Shiley prosthesis, the ventricular septal defect was closed with a patch, and the pulmonary stenosis was relieved with an outflow patch. Four years later she had a further episode of endocarditis caused by *Staphylococcus aureus*. This was successfully treated medically. When she was 13 right heart failure developed. This was caused by subacute obstruction of the Björk-Shiley valve, which was replaced with a 29 mm Ionescu-Shiley bioprosthesis. Postoperatively bradycardia developed and because of this a permanent epicardial pacemaker was implanted. Atrial fibrillation developed when she was 18.

Physical examination showed an irregular pulse of 75 beats/min, a blood pressure of 115/70 mm Hg, bilateral pitting oedema to the waist, 15 cm elevation of the jugular venous pulse, 3 cm hepatomegaly, and mild ascites. A left parasternal heave was noted, and

on auscultation both heart sounds were single, with a grade 2/6 pulmonary ejection murmur, a grade 1/6 pulmonary early diastolic murmur, and a grade 2/6 tricuspid diastolic murmur. The chest x ray showed cardiomegaly with right atrial enlargement and normal lung fields. The electrocardiogram showed atrial fibrillation with paced ventricular rhythm and occasional ventricular extrasystoles. The echocardiogram showed good left ventricular function and mildly impaired right ventricular function; and colour Doppler scanning showed a narrow, turbulent, high velocity jet through the tricuspid valve with minimal tricuspid valve regurgitation. There was no evidence of right ventricular outflow obstruction. Doppler measurements are given in the table.

Cardiac catheterisation was performed under local anaesthetic without sedation. Haemodynamic data are given in the table. The interatrial and interventricular septa were intact. The leaflets of the tricuspid valve prosthesis did not show calcification on fluoroscopy. A right ventricular angiogram showed slight dilatation of the ventricle and slightly impaired systolic function with a trace of tricuspid valve regurgitation.

A catheter with a 20 mm diameter balloon (Mansfield Scientific, Mansfield, MA) was introduced via the femoral vein. The balloon was centred through the prosthesis and inflated to maximum diameter on four occasions for 15-25 seconds (figure). During balloon inflation there was no fall in systemic arterial pressure, no impairment of consciousness, and no cyanosis—despite the fact that the interatrial and

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Table Doppler echocardiographic and haemodynamic data

	First dilatation			Second dilatation		
	Before	After	Follow up	Before	After	Follow up
Weight (kg)	61.7	57.6*	55.0	61.4	57.4*	59.8
Heart rate (beats/min)	70	70	74	70	70	70
Blood pressure (mm Hg)	120/54	117/52	115/55	110/48	120/60	125/60
Doppler:						
TV $\frac{1}{2}$ T (ms)	748	493*	646	686	472*	635
Cardiac catheterisation:						
RA (mean) (mm Hg)	15	14	—	17	16	—
RV (mm Hg)	30/4	36/8	—	30/7	34/12	—
TVEDG (mm Hg)	8–10	4–6	—	9–11	4–8	—
CI (l/min/m ²)	3.4	3.2	—	2.8	2.8	—
TVA (cm ²)	0.52	0.65	—	0.43	0.58	—

*Measured 24 hours after dilatation.

CI, cardiac index; RA, right atrial pressure; RV, right ventricular pressure; TVA, tricuspid valve area; TVEDG, tricuspid valve end diastolic gradient; TV $\frac{1}{2}$ T, tricuspid valve pressure half time.

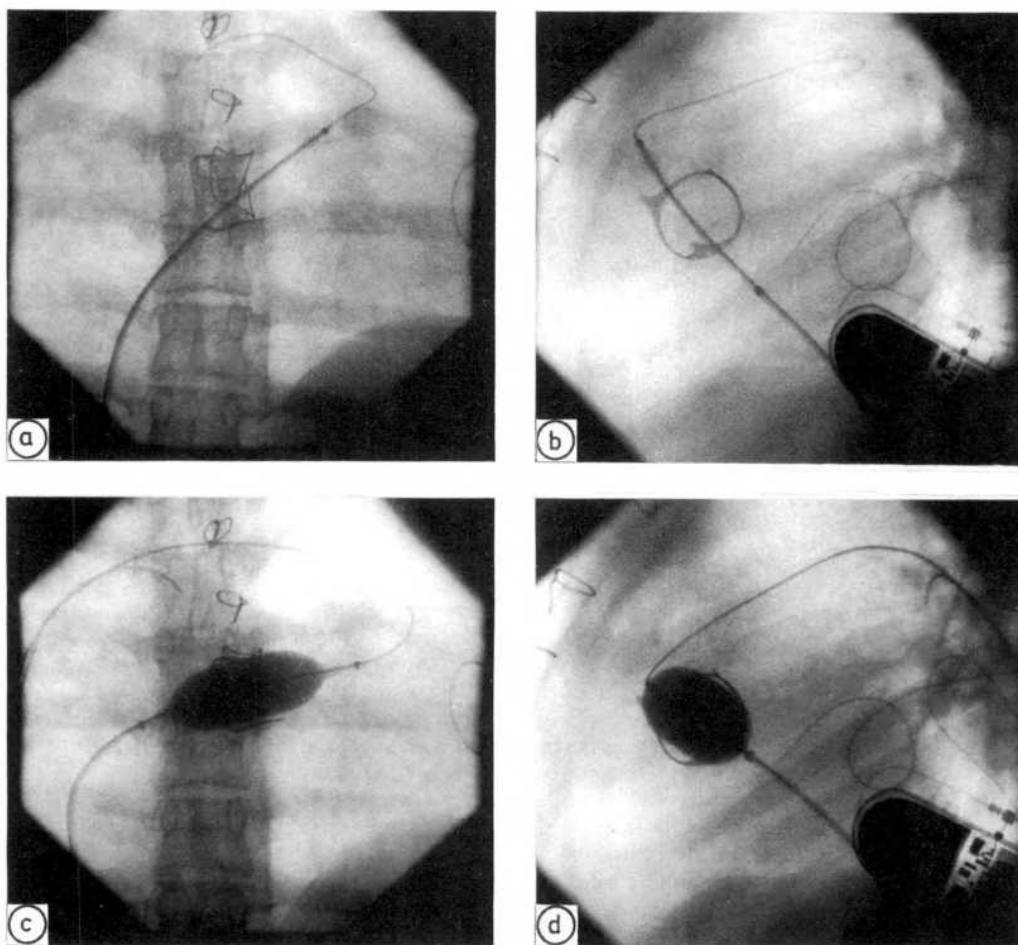


Figure (a) Anteroposterior and (b) lateral views of the deflated balloon catheter positioned through the tricuspid valve prosthesis. (c) During inflation the balloon reached a maximum diameter (20 mm) without "waisting" and (d) seemed to occlude the valve completely.

interventricular septa were intact and the balloon seemed to occlude the prosthetic valve completely. Haemodynamic measurements were repeated (table) and a repeat right ventricular angiogram showed no increase in the severity of the tricuspid regurgitation.

In the first 24 hours after the procedure the patient experienced a considerable diuresis and lost 4 kg in weight. At follow up five weeks later there had been a further reduction in weight with an appreciable improvement in symptoms. Over the following three months there was a gradual return of symptoms and an increase in weight to the first preadmission level. The physical signs of right heart failure with ascites had returned and Doppler echocardiography again confirmed severe stenosis of the tricuspid valve prosthesis (table).

The patient was readmitted and underwent repeat catheterisation. Haemodynamic data are given in the table. The balloon dilatation was repeated with a 23 mm diameter balloon, which was inflated to maximum diameter on two occasions for 30 seconds. Again there was no fall in systemic pressure during maximum balloon inflation. Repeat haemodynamic data are given in the table. A repeat right ventricular angiogram showed only a trace of tricuspid valve regurgitation.

After the second procedure there was a 4 kg weight loss overnight as a result of considerable diuresis. The improvement in symptoms was maintained for six months before the symptoms and signs of right heart failure returned. Further balloon dilatation was thought unlikely to produce a lasting improvement in symptoms and the patient underwent reoperation. The right atrium contained a large organised thrombus (7 cm × 4 cm × 4 cm). When the tricuspid prosthesis was excised its leaflets were found to be very stiff with calcific vegetations on both atrial and ventricular surfaces. There was no cusp fusion and no evidence of damage from balloon dilatation. A St Jude prosthesis was implanted and recovery was uneventful.

Discussion

Percutaneous balloon dilatation was offered to this patient as an alternative to valve replacement because she was young and had already undergone tricuspid valve replacement twice. The aim was to produce acceptable palliation rather than permanent relief of the valve stenosis. If the effect of balloon dilatation had persisted, insertion of a mechanical prosthesis

(necessitating oral anticoagulation) might have been delayed until after childbearing.

The mechanism of the partial relief of the obstruction is unclear. The leaflets of the bovine pericardial prosthesis were very stiff and balloon dilatation probably stretched or otherwise reduced the stiffness of the valve leaflets.

Balloon dilatation of a tricuspid valve prosthesis has been reported once before. Feit *et al* produced apparently successful palliation in a patient with a 31 mm Hancock porcine prosthesis.¹ Their patient was followed up for only one month and so it is not clear whether the benefit persisted. They noted a fall in right atrial pressure and an increase in cardiac index, whereas in our patient there was no change in cardiac index and we saw an increase in right ventricular end diastolic pressure rather than a fall in right atrial pressure after balloon dilatation.

McKay *et al* reported two patients who underwent balloon dilatation of an aortic valve bioprosthesis.² The procedure was complicated by severe damage to the prosthesis and one patient died as a result. They suggest that contraindications to dilatation of prosthetic valves should include valve leaflet calcification, the presence of vegetations or thrombosis, and degenerative changes in the valve cusps.

Lloyd *et al* reduced valvar gradients in three of five patients undergoing balloon dilatation of calcified stenotic bioprosthetic valves in right ventricle to pulmonary artery conduits but no follow up data were given.³

Our experience suggests that the role of balloon dilatation in the management of stenosed bioprosthetic valves will be limited. Although symptoms and haemodynamic function may be improved, lasting benefit is unlikely.

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Obituary

William Evans

The son of a farmer, William Evans was born in 1895 at Tregaron, Cardiganshire, and died on 20 September after a span of almost 93 years.

After preliminary education at the local school he won an entrance scholarship in Greek to Lampeter Divinity College but did not accept it on the disestablishment of the Church in Wales. Instead he became a clerk in Lloyds Bank in 1914 but after one year he joined the Army as a private. Later during combatant service in France he served as an infantry officer in The Lancashire Fusiliers and became battalion education officer. After returning from the Army he decided to take up medicine, entering the University College of Wales at Aberystwyth and subsequently The London Hospital Medical College in 1920. He won important undergraduate prizes and qualified in 1924. The following year he obtained the MB, BS with distinction in surgery, and proceeded to the MD in 1927, MRCP in 1928, and was elected fellow of the Royal College in 1935. In 1944 the University of London awarded him the degree of DSc.

He held several house appointments at The London Hospital including the post of assistant in the pathology department which he regarded as important because "The clinician has to search the truth from his patient; the pathologist has the stark truth before him". He was elected honorary assistant physician and assistant director of the Medical Unit in 1934. After four years in general medicine he was appointed assistant physician to the cardiac department—a department of international reputation made so by Sir John Parkinson, himself a disciple of Sir James Mackenzie. Later William Evans became physician to that department and was appointed physician to the National Heart Hospital and the Institute of Cardiology. The prestige of the cardiac department at The London was maintained and enhanced by him for 22 years until his retirement from the staff in 1960. He was honorary consultant cardiologist to the Royal Navy from 1946 to 1967 and at some time held a similar appointment to the Royal Society of Musicians. He was a founder member of the British Cardiac Society in 1937 and later an honorary member. He was on the council of the society from 1942 to 1946 and from 1956 to 1960, and its Chairman in 1965, and was also a member of the



American Heart Association. He was one of the prime instigators of the British Heart Foundation.

From 1929 to 1966 his contributions to medical literature were vast and probably unique during this era. He wrote at least 100 scientific papers in many national and international journals including 41 in the *British Heart Journal*. He also published five books *Student's Handbook of Electrocardiography* (1934), *Cardioscopy* (1952), *Cardiography* (2nd edition 1954), *Cardiology* (2nd edition 1956), and *Diseases of the Heart and Arteries* (1964). These contributions were all clear, concise, and persuasive—always written in a distinctive and well recognised style indicating clarity and precision of thought. Following upon meticulous and careful personal research and blessed with immaculate handwriting the production of a scientific paper presented no problems to William Evans; indeed he seemed to regard it as a hobby and never a burden. This remarkable gift remained with him throughout his life and was the envy of less fortunate contributors. His paper on "Congenital stenosis (coarctation) atresia and interruption of the aortic arch" (1933) is still a classic and so were his papers on the comparative values of various drugs. His original observations on the "Electrocardiogram in

Friedreich disease" (1942), "The heart in myotonia atrophica" (1944), "Familial cardiomegaly" (1949), and "Alcoholic myocardiopathy" (1961) bear witness to his knowledge of general medicine, his powers of recognition, and the ability to record them. Some of his papers were provocative but always stimulating, and most were major contributions to our knowledge of heart disease. Not all would agree with what he wrote or said but all cardiologists respected him for his honesty, sincerity, common sense, and the ability to convey a message. His lectureships included Strickland Goodall (1942); Finlayson (1947); St Cyres (1952); Gerish Milliken, University of Philadelphia (1954); First Rufus Stolz Memorial, University of Evanston, Illinois (1954); Carbutt Memorial (1957); Schorstein (1961); Wiltshire (1961); First Leonard Abrahamson Memorial, Royal College of Surgeons of Ireland, Dublin (1963); and Sir Thomas and Lady Dixon, Belfast (1965). He was also guest lecturer at the centenary meetings of the Royal Melbourne Hospital in 1948. He received the Sydney Body gold medal in cardiology in 1954. William Evans was awarded an honorary fellowship of the Royal Society of Medicine in 1976. Such honorary fellows are selected from among persons who have distinguished themselves eminently in the service of medicine and the branches of science allied to it.

As well as being a prolific writer he was in the opinion of his students, assistants, and colleagues the greatest teacher of British cardiology of his time. Those privileged to be so instructed will always remember him as a master exponent of the art of bedside teaching—clear, practical, relevant, and somewhat dogmatic but never overlooking the patient to whom he was always kind, sympathetic, and reassuring. He always stressed that "No patient should be the worse for seeing his doctor". He certainly practised what he preached. He insisted that the students should have a "little book" so that short notes could be made during instruction. Invariably these notes included one of his profound quotations. Some have treasured and kept the "little book" and decades later have reread it and marvelled at the recorded truths which had stood the test of time. Those fortunate enough to have been taught by William Evans and become themselves clinical teachers have tried to emulate him to the undoubted benefit of innumerable students throughout the land. William Evans never believed in the use of anticoagulants in the treatment of cardiac infarction—he called them "rat poisons" and never prescribed them. Upon hearing in 1974 that they had gone out of favour he observed "Someone tried hard to stop them coming in twenty years before". At one time he had a serious surgical illness which neces-

sitated two periods as an inpatient. Of this experience he concluded that "Every doctor should welcome incarceration in a hospital bed for a short time. Not till then will his medical education be complete".

In 1967 he ceased the practice of cardiology, left London, and returned to his place of birth. Looking out of his windows he could see the river Teifi flowing gently as it curved around the meadows with the land beyond it rising into the hills—the landscape he knew so well as a child. He had now retired and of retirement he had this to say "Retirement marks the end of gainful employment, but it is the port of entry into a period of rewarding enjoyment; an emergence from the competitive race with its hazards and its hurdles into the calm fields which provide for contemplative soliloquy". He most certainly enjoyed it. He married relatively late in life but unfortunately his charming and delightful wife Christina died suddenly in 1964. He lived on his own in his bungalow without any domestic or other help and his friends were concerned about possible loneliness but his answer was "Loneliness as a lone complaint is a preventable illness and its specific antidote is continued occupation". The lure of the land had a magnetic influence upon him; thus he spent his time helping on the farm, tending to the cows and sheep, and building stone walls and sheds—indeed he was a gifted artisan with special affinity for stonemasonry. He enjoyed gardening and was an astute fisherman "It is not the type of fly that is important but the way it is presented to the fish". His working days were long and full and in the evenings he would write out the work for the morrow and would say "Plan today, plod tomorrow". After the day's physical toil he continued to write and published the diaries of his grandfather who had emigrated to Australia. *The Diary of a Welsh Swagman* (1975) won the approbation of the Australian Education Authority and included it as part of their curriculum in Australian history. He completed four other books as well as a volume of 41 poems. Always working, reading and writing, maintaining his home, cooking and cleaning, he had no time for television. A few of his past assistants, all members of the British Cardiac Society decided to buy him a set as a birthday present, but the bearer of the gift was sent back from whence he came and was told that the prospective recipient had better and more constructive things to do and that his main philosophy of life was "Compulsive contemplation and compulsive occupation". Willie, as he was affectionately known, had a rich vein of kindness and humility in his character, always so gentle, compassionate, and courteous to all, especially to his patients. His sayings—"It is better to do nothing than something when nothing needs to be done" and "Among the many medicaments which doctors carry in their bags, there

Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre, London, on Tuesday to Thursday, 22 to 24 November 1988. The President, E SOWTON, took the Chair during private business. D A CHAMBERLAIN was chairman of the scientific programme.

Abstracts of papers

ISIS-2: a large randomised trial of intravenous streptokinase and oral aspirin in acute myocardial infarction

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A total of 17 189 patients entering 417 hospitals up to 24 hours (median five) after the onset of suspected acute myocardial infarction were randomised, with placebo control, to receive either ((a) a one hour intravenous infusion of 1.5 million units of streptokinase; or (b) one month of 160 mg/day enteric-coated aspirin; or (c) both active treatments; or (d) neither. Each agent produced a highly significant reduction in five week vascular mortality: 774 (9.2%) vascular deaths among patients allocated aspirin *v* 954 (11.4%) among those allocated placebo tablets (odds reduction: 21% (5); $2p < 0.0001$); 747 (8.9%) among patients allocated streptokinase *v* 981 (11.7%) among these allocated placebo infusion (odds reduction: 26% (4); $2p < 0.0001$). The combination of streptokinase and aspirin was significantly better than either agent alone, and their separate effects on mortality seemed to be additive: 327 (7.8%) vascular deaths among patients allocated both active agents *v* 534 (12.8%) among these allocated neither (odds reduction: 42% (6); 95% confidence intervals 33 to 49%; $2p < 0.001$). There was evidence of benefit from each agent even for patients treated late after pain onset (odds reduction at 0.4, 5-12, and 13-24 hours: 22% (7), 21% (7), and 17% (13) for aspirin alone; 37% (6), 15% (7), and 22% (12) for streptokinase alone; and 52% (6), 32% (9), and 37% (16) for the combination of streptokinase and aspirin). Aspirin significantly reduced non-fatal reinfarction (49% (9) reduction) and non-fatal stroke (37% (17) reduction) in hospital and was

not associated with any increase in cerebral haemorrhage or bleeds requiring transfusion. Streptokinase was associated with more bleeds requiring transfusion (0.4% excess) and cerebral haemorrhage (0.1-0.2% excess), but with fewer other strokes.

There were significantly fewer reinfarctions, strokes and deaths among patients allocated the combination of streptokinase and aspirin than among those allocated neither. A median of 15 months follow up indicated that the differences in early mortality also have a long term effect.

Anglo-Scandinavian study of early thrombolysis with recombinant tissue plasminogen activator(rt-PA): a six month mortality study

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A group of 13 323 patients with suspected acute myocardial infarction admitted to 53 coronary care units were considered for entry to a prospective double blind placebo controlled trial of recombinant tissue plasminogen activator (rt-PA) given within five hours of onset of major symptoms. 5016 (38%) of the patients were randomised to receive rt-PA or placebo. Of the remainder, 72% were excluded on the basis of time, and all the excluded patients were documented. Treatment began with an intravenous bolus of heparin 5000 units, followed by a bolus of rt-PA 10 mg (or placebo), then rt-PA 90 mg intravenously given as 50 mg in the first hour and 20 mg in each of the next two hours. All patients received heparin 1000 iu/hour for the next 21 hours. The trial infusion was prematurely terminated in 5% of the rt-PA group and 2.5% of the placebo group, the excess in the rt-PA group being mainly for bleeding complications. During the subsequent heparin infusion a further 6% were withdrawn in the rt-PA group and 3.5% in the placebo group. The one month overall mortality was 7.2% in the rt-PA group compared with 9.9% in the placebo group (relative reduction 26%, 95% CI 11 to 38%). About 70% of patients in both groups were diagnosed in

hospital as having had an acute myocardial infarction, and their one month mortalities were rt-PA 9%, and placebo 13% (relative reduction 28%, 95% CI 14 to 41%). The six month follow up concludes in August 1988.

Interim analysis of the six month outcome in 2607 patients shows an overall mortality of 7.9% in the rt-PA group and 10.3% in the placebo group. Thus early treatment with rt-PA saves lives but carries a similar risk of bleeding complications as streptokinase.

Comparative one year mortality in patients treated with thrombolytic treatment at home and in the coronary care unit

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Eighty six patients with acute evolving myocardial infarction were seen by the Mobile Intensive Coronary Care Unit (MICCU) within six hours of the onset of symptoms. They were given 1.5 million units of streptokinase over 30 minutes. Thirty patients (mean age 60 years) were given streptokinase at home. The remainder (mean age 58.5 years) were treated in the coronary care unit (CCU). Previous history of ischaemic heart disease was 56.7% (MICCU group) and 51.8% (CCU group). Mean delay times for the two groups were 130.6 minutes (MICCU) and 178.4 minutes (CCU) ($p = < 0.01$). Reperfusion times, judged clinically and electrocardiographically, were 83.8 minutes (MICCU) and 94.2 minutes (CCU). The inpatient vascular mortality for the MICCU group was 3.3% compared with 10.7% for the CCU group. The one year vascular mortality was 6.7% for those treated by the MICCU and 21.4% for those in the CCU ($p = < 0.05$). There were no adverse events in either treatment group.

These data suggest that intravenous thrombolysis given outside hospital can provide a further reduction in mortality after acute myocardial infarction.

Comparison of recombinant tissue plasminogen activator and streptokinase for preservation of left ventricular function after myocardial infarction

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Streptokinase (SK) and recombinant tissue plasminogen activator (rt-PA) have been compared in terms of infarct artery patency after an acute coronary artery occlusion but there are few comparative data for effects on left ventricular function. In a double blind trial 244 patients presenting within three hours of a first infarction were randomised to streptokinase (1.5×10^6 u over 30 minutes) or to rt-PA (100 mg over three hours). Heparin was given for 48 hours. Aspirin and persantin were given on admission and continued until cineangiography was performed three weeks later. There were similar effects on left ventricular function: ejection fraction 58% (12%) SK, *v* 58% (13%) rt-PA; end systolic volume 63 (29) ml SK, *v* 66 (31) ml rt-PA. There was no difference in the frequency of bleeding (one patient had a cerebral haemorrhage after administration of rt-PA for reinfarction three weeks after receiving streptokinase.) Reinfarction rates were also similar (7% SK *v* 5% rt-PA). There was a higher 30 day mortality (7.8% *v* 1.7%) and a higher incidence of hypotension (21% *v* 8%) in streptokinase treated patients.

The effects of streptokinase and rt-PA on preservation of left ventricular function are similar.

Coronary lesion morphology in patients with acute myocardial infarction treated with streptokinase

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After thrombolysis for acute myocardial infarction (MI) there is a high incidence of recurrent angina and reinfarction. Morphological features of the coronary lesions may reflect their unstable nature, and predict the future clinical course. Quantitative angiography was performed in 50 patients, two to four days after streptokinase (SK) treatment for acute MI; a control group of 18 patients with stable angina was matched for age and sex. In the SK group, the infarct associated artery was patent in 36 (72%) and occluded in 14; in the control group there were three occlusions and 22 other important stenoses. There were no differences in stenosis length, severity, calcification or location of patent lesions at an acute bend or at a branch point. Lesions in the SK group were more often irregular ($p < 0.001$), eccentric ($p < 0.001$), had a shoulder ($p < 0.001$), and had globular filling defects ($p < 0.025$), and linear filling defects ($p < 0.005$). A previously described index of plaque ulceration was higher in the SK group (6.7 (9.7) *v* controls 3.2 (3.1), $p < 0.01$). Subsequently 13

of the 50 SK patients were maintained on heparin infusion until PTCA three to five days later. At repeat angiography immediately before PTCA, globular filling defects seen in four had all disappeared, whereas linear filling defects originally seen in six persisted in three. Fewer lesions were irregular ($p < 0.005$) and the ulceration index decreased from 9.3 (15.4) to 2.8 (1.6) ($p < 0.01$).

These data show that lesions in the infarct associated artery after SK treatment are particularly irregular, with filling defects, perhaps corresponding to plaque fissuring and intraluminal thrombosis; these features partially resolve with maintenance heparin infusion.

Inhibition of coronary thrombosis with low dose tissue plasminogen activator (t-PA): the potential for modifications of endogenous t-PA activity

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t-PA is an endogenous protease with high affinity for fibrin bound plasminogen. Its concentration varies diurnally and in response to a variety of stimuli and it may be implicated in the homeostasis of thrombosis and thrombolysis in man. We and others have shown the effectiveness of therapeutic doses of t-PA in inducing coronary thrombolysis in experimental animals and in man. We hypothesise that doses of t-PA insufficient to induce effective thrombolysis might nevertheless inhibit clot formation in vivo because of its high affinity for nascent fibrin, but not fibrinogen. To test this hypothesis we studied the action of 10 000–200 000 IU/ml t-PA (6000–100 000 ng/ml) on thrombin clots using pooled citrated plasma, or euglobulin fractions from normal human subjects. The concentration of t-PA required to achieve the half maximum rate of lysis was reduced from 650 to 260 ng/ml for euglobulin fractions ($n = 158$), or from 6800 ng/ml to 2670 ng/ml for whole plasma containing endogenous plasmin inhibitors ($n = 158$). The studies were confirmed in vivo with 23 dogs. Coronary thrombosis (induced by the potent thrombogenic stimulus of a non-occlusive intra-coronary copper coil) was inhibited by t-PA at concentrations of 140–430 ng/ml ($n = 6$) (but not at < 140 ng/ml, $n = 12$), and totally prevented at > 460 ng/ml ($n = 5$).

We conclude that low, sub-thrombolytic doses of t-PA can inhibit thrombus formation. This raises the therapeutic possibility of administering low-dose

t-PA or augmenting endogenous t-PA activity in patients at high risk for occlusive thrombus formation.

Enterovirus RNA in myocardium of patients with dilated cardiomyopathy

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Two groups of patients with dilated cardiomyopathy (DCM) were studied. One was diagnosed clinically by haemodynamic function and angiography and proved by left ventricular biopsy. The second had end stage DCM and underwent orthotopic cardiac transplantation. Endomyocardial biopsy samples taken from group I at the time of diagnosis and tissue from the explanted hearts of group II were examined for virus RNA by molecular hybridisation with an Enterovirus group specific probe. In group I, biopsy specimens from 19 of 53 (36%) DCM patients were positive for virus RNA compared with none of 37 controls with other, specific heart muscle diseases ($p = < 0.0002$). In group II, tissue from six of 21 (29%) explanted hearts from patients with cardiomyopathy were positive for virus RNA compared with one of 19 controls with ischaemic heart disease ($p = < 0.05$).

These data show that Enterovirus RNA is present in myocardium in a large proportion of patients with DCM and can persist until end stage disease. This association implicates Enterovirus infection in the pathogenesis of DCM.

Novel cardiac specific circulating autoantibodies in dilated cardiomyopathy

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Organ specific autoimmunity is characterised by circulating autoantibodies that are specific to the diseased target organ and do not cross react with other tissues. Organ specific cardiac antibodies have not been reported. To determine whether organ specific cardiac antibodies are present in dilated cardiomyopathy, we tested 55 serum samples from patients with dilated cardiomyopathy, 225 with other cardiac disease, 166 from patients with polyendocrine autoimmunity without overt cardiac disease, and 200

normal subjects by indirect immunofluorescence on human atrium and skeletal muscle. Organ specific cardiac antibodies were more common ($p < 0.01$) in dilated cardiomyopathy (10/55, 18%) and in polyendocrine autoimmunity (31/166, 19%) than in patients with other cardiac disease (2/225, 1%) and normal subjects (6/200, 3%). Organ specific cardiac antibodies were IgG (titre range 1/10 to 1/80) and gave a cytoplasmic immunofluorescent staining only on heart tissue. Non-organ specific cardiac antibodies showed a sarcolemmal and striated immunofluorescent pattern both on the heart and on skeletal muscle, but in contrast to organ specific cardiac antibodies were detected with a similar frequency in dilated cardiomyopathy (6/55, 11%), polyendocrine autoimmunity (15/166, 9%), other cardiac disease (13/225, 6%), and in normal subjects (13/200, 6.5%).

These results support the existence of organ specific cardiac antibodies in dilated cardiomyopathy and suggest an autoimmune pathogenesis in some patients with this condition.

Is syndrome X a variable degree of myopathy?

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Syndrome X has been used to describe patients who complain of typical angina but have arteriographically normal coronary vessels. Between 1985 and 1988, 100 randomly selected patients with typical angina were studied, in whom musculoskeletal and gastrointestinal explanations for chest pain had been excluded. Of the patients, 58% were female and the age range was 29 to 64 years. None of the patients had evidence of obstructive coronary lesions at angiography, although in three patients ventricular function was somewhat reduced. Maximal symptom limited exercise tolerance tests were positive in 31% (ST shift > 1 mm). Gated thallium scans were abnormal in 98%, with patchy defects affecting predominantly the septum and inferior surfaces. The distributions of defects were similar to those seen in patients with established myopathy, but could be clearly differentiated from scans obtained from normal volunteers ($p < 0.01$). The extent of left ventricular impairment was assessed quantitatively by two observers dividing the left ventricular region of interest in three projections (anterior, 40°, and 70° left anterior oblique) into a total of 45 segments. In those patients with positive exercise tests, mean left ventricular involvement was 33 (9%) compared with

28 (7%) ($p < 0.05$) when the exercise test was negative.

These results suggest that syndrome X may be a form of myopathy with a positive exercise test reflecting more substantial impairment of the myocardium.

Evidence for an abnormal vasodilator response in hypertrophic cardiomyopathy

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Sudden death is common in hypertrophic cardiomyopathy (HCM) but the mechanisms(s) have not yet been established. To identify those at risk of haemodynamic collapse, 103 patients with HCM, age 12–70 years (mean 40) underwent symptom limited treadmill exercise with standard cuff blood pressure recording (BP) at each minute of exercise and every 15 seconds during recovery for three minutes on at least two occasions. The test was repeated in 25 of the patients with direct arterial pressure measurement. Fifty one had normal, and 52 abnormal, BP responses with either hypotension during recovery or a fall during exercise of ≥ 20 mm Hg (range 20–100, mean 45 mm Hg) from the peak value to that recorded immediately before stopping. A family history of sudden death was more common in those with an abnormal exercise BP response (24/52 *v* 3/51, $p < 0.001$). To assess the mechanism of the hypotensive response, 10 with abnormal and seven with normal exercise BP responses underwent exercise haemodynamic studies, with continuous direct arterial pressure recording and measurement of cardiac output each minute. Systolic BP fell by 25–95 (mean 50) mm Hg in all 10. The rise in cardiac index on exercise (1/minute/m²) was similar in those with normal (2.3 (0.5) to 8.8 (2.4)) and abnormal BP response (2.1 (0.5) to 7.2 (1.1)). Systemic vascular resistance in the two groups at rest and after two minutes of exercise was similar, but at peak exercise fell significantly more in the hypotensive *v* normal BP responders (22 (6)% *v* 42 (4)% of resting values, $p < 0.01$). To assess the mechanism of this abnormal vasodilation, forearm plethysmography was performed during supine bicycle exercise in 11 hypotensive patients and 10 normal volunteers. Forearm vascular resistance fell by 18 (45)% in the hypotensive patients, but increased by 131 (45)% in the normal volunteers ($p = 0.003$).

Exercise hypotension is common in HCM, is strongly associated with a family history of sudden death, and is due to an inappropriate vasodilation of non exercising vascular beds.

Objective assessment of exercise capacity in hypertrophic cardiomyopathy: association with clinical and prognostic features

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Symptom limited treadmill exercise testing was performed in 91 consecutive patients with hypertrophic cardiomyopathy (age 12–70, mean 40 years) with objective assessment of exercise capacity by maximal oxygen consumption (VO_2 max) and ST segment and blood pressure monitoring. An abnormal fall in BP on exercise was seen in 47/91. ST segment changes were common (ST depression in 30 and pseudonormalisation of T waves in 11). Exercise capacity was abnormal even in NYHA Class I patients who had a VO_2 max of 28.5 (7.8) (normals > 40), and was significantly lower in those with dyspnoea Class II and III (20.8 (5.6), $p < 0.001$). VO_2 max was lower in patients with chest pain (22.6 (5.4)) *v* those without (26.3 (8.6)) $p < 0.05$, and in those with non-sustained ventricular tachycardia on 24 hour ECG monitoring (21.5 (5.6)) *v* those without (26.2 (7.6)); $p < 0.01$). VI_2 max was related to age ($r = -0.47$, $p < 0.001$) and left atrial dimension ($r = -0.43$, $p < 0.001$). Reduced VO_2 max, abnormal BP response, and ST segment changes were not associated with maximum LV wall thickness, presence or magnitude of left ventricular gradient, conventional radionuclide indices of systolic and diastolic function, or to Doppler indices of diastolic function. A family history of sudden death was significantly more common in those exhibiting a hypotensive exercise response and those with pseudonormalisation of T waves. ST segment changes, however, were not associated with exertional chest pain.

In conclusion, exercise capacity was reduced even in symptom free patients with hypertrophic cardiomyopathy and was not associated with conventional indices of diastolic or systolic function, including the presence or magnitude of gradients. The association of a reduced VO_2 max, a hypotensive response, and pseudonormalisation of T waves with markers of adverse prognosis suggests a potentially important role of exercise testing in the assessment of high risk patients with hypertrophic cardiomyopathy.

Hypertrophic cardiomyopathy without hypertrophy: a description of two families with premature cardiac death and myocardial disarray in the absence of increased muscle mass

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The necropsy finding of widespread myocardial disarray typical of hypertrophic cardiomyopathy in three macroscopically normal hearts prompted clinical evaluation of the two families. In family A, the propositus, her daughter, sister, and nephew died suddenly, aged 37, 21, 42, and 17 years, while in family B only the propositus died a premature cardiac death at the age of 45. Eleven of the surviving first degree relatives were investigated. They were aged 12–49, median 18 years. Six had normal clinical cross sectional echocardiographic and radionuclide (Tc) findings. Five were symptom free but had electrocardiographic abnormalities including atrial fibrillation ($n = 1$), left axis deviation ($n = 2$) and widespread repolarisation changes ($n = 5$), with normal echocardiographic wall thickness and cavity dimensions, and radionuclide indices of left ventricular function. Three of the five patients with abnormal electrocardiograms had dilated left atria associated with abnormal echocardiographic left ventricular relaxation and filling patterns.

The finding of myocardial disarray in the absence of left ventricular hypertrophy and in association with repolarisation changes in two families is consistent with a wider spectrum of hypertrophic cardiomyopathy than has been recognised, and suggests that hypertrophy may be a secondary rather than a primary abnormality in this condition.

Magnetic resonance imaging of the great arteries in infants

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Fifty two infants (age range 1–50 weeks) with congenital heart disease were studied with magnetic resonance (MR) imaging. A 1.5 T whole body MR imaging system was used with patients sedated and positioned supine inside a 32 cm diameter head coil. Multiple electrocardiographic gated sections 5 mm thick were acquired using a spin echo sequence with echo time of 30 milliseconds. A combination of standard and oblique imaging planes were used. Echocardiographic studies had previously been

performed in all cases. Ventriculoarterial connections were defined in all 46 patients in whom full intracardiac imaging was performed. They were identified as concordant in 33 patients and discordant in five. Two patients had double outlet right ventricle (DORV), one a common arterial trunk, and five patients had pulmonary atresia. The aorta was identified posteriorly to the pulmonary artery in 38 patients, anteriorly in three, and to the left in the patient with DORV. In the patient with a common arterial trunk a single pulmonary trunk was identified arising anteriorly from the main trunk. Of the two patients with Fallot's tetralogy the pulmonary trunk and branch pulmonary arteries were identified as hypoplastic in one, and normal in the other. In five patients with pulmonary atresia, confluent central pulmonary arteries were identified in three cases and were considered absent in two. Aorto-pulmonary collateral vessels were found in two cases. Aortic structure was clearly shown. An aberrant right subclavian artery, a large arterial duct, a double aortic arch and 14 cases of aortic coarctation have all been identified.

MR images provided consistently greater detail than echocardiography and appeared particularly suitable for imaging the great arteries, superseding the need for angiography in many instances.

Childhood blood pressure measurements in nine British towns

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Striking differences in the average blood pressure of middle aged men in 24 British towns have been reported. This study aimed to establish whether a similar pattern of differences could be detected in children 5-7 years of age in nine of the original 24 towns. Three towns with high, three with intermediate, and three with low average adult blood pressures were chosen. In each town stratified random sampling was used to select 500 children. Blood pressure was measured with a Dinamap 1846SX oscillometric blood pressure recorder. The overall response rate was 85.7% ($n = 4114$). Average blood pressures varied by 5.6 mm Hg (systolic) and 4.5 mm Hg (diastolic) between the highest town (Merthyr Tydfil) and the lowest (Guildford). The extent of variation was unlikely to be due to chance ($p < 0.0001$). Overall age standardised mean systolic pressures in the three towns with high adult blood pressure measurements combined were 2.35 mm Hg (95% CI 1.71 to 3.02; $p < 0.001$) higher than in those with low adult pressure measurements com-

bined; the towns with intermediate adult pressures were in an intermediate position. The findings were not explained by observer bias nor by temperature differences between the towns.

The presence of geographical differences in blood pressure in 5-7 year olds resembling the adult pattern implies that the determinants of population blood pressure differences are present at an early age and that further aetiological studies should focus on the first decade of life.

Transoesophageal echocardiography, an improved diagnostic technique for subaortic membranes

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Fifteen adults with subaortic membranes underwent precordial and transoesophageal (TEE) studies to compare and contrast the information derived from cross sectional echocardiography and colour flow imaging (CFI). Precordial cross sectional echocardiography clearly showed the membrane septal origin in 11 patients but showed the lateral insertion in only eight. Precordial CFI studies clearly identified the site of left ventricular outflow tract turbulence in 14, but could not distinguish this abnormal flow pattern from that of hypertrophic obstructive cardiomyopathy or a fibromuscular tunnel. TEE in 15 patients clearly visualised the entire membrane, showing a wider range of both lateral and septal insertion patterns than that suspected by precordial echocardiography. Septal insertion varied from 0.1 to 4.3 cm below the aortic valve. Lateral insertion varied from (a) the aortic leaflets, (b) the left ventricular outflow tract lateral wall, (c) mitral chordae, or (d) reduplicated mitral tissue. CFI clearly defined both the obstruction site and minimal jet width. Associated mitral incompetence was accurately diagnosed and traded by CFI in 10/15 by TEE in contrast to 2/15 by precordial echocardiography. There was a similar diagnostic improvement in evaluating the nature and severity of associated aortic valve lesions. In four patients the information derived from the transoesophageal study subsequently proved invaluable in intraoperative decision making.

We conclude that TEE provides important additional morphological and haemodynamic information over precordial echocardiography in this lesion.

Acceleration time in the aorta and pulmonary artery in prenatal life and in the newborn in the first week of life

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Acceleration time was measured by Doppler echocardiography in the aorta and pulmonary artery in 102 normal human midtrimester fetuses, in 45 fetuses with gestational ages from 30–40 weeks, in 45 babies born at full term and 24 hours of age, and 80 neonates during the first week of life. Each fetus and neonate had a normal cross sectional echocardiogram. The Doppler sample volume was placed in the pulmonary artery and aorta, parallel to blood flow. The blood flow velocity wave form was displayed and recorded on videotape with the tracing speed set at 100 mm/second. The measurement of time to peak velocity (TTPV) was obtained subsequently from a frozen image from the videotape in 10 cardiac cycles, and the mean was obtained. The TTPV in the pulmonary arteries of fetuses of 30–40 weeks' gestation was no longer than in the midtrimester fetuses, although not significantly different from that in the aorta for the same gestational age. TTPV in the aorta did not show any significant alteration throughout pregnancy. In postnatal life TTPV in the pulmonary artery was much longer than in prenatal life.

These results suggest that the resistance faced by the right ventricle is higher than that faced by the left ventricle and diminishes progressively throughout pregnancy. The greatest fall in pulmonary artery pressure occurs after birth during the first day of life.

Percutaneous balloon dilatation for critical pulmonary stenosis in neonates and infants

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The role of balloon dilatation (PBV) in neonates and infants with critical pulmonary stenosis is unclear. We attempted PBV in 13 patients (median age 14 days, range 1 day to 9 months) with systemic or suprasystemic right ventricular systolic pressures, mean (SEM) ratio 1.3 (0.1), caused by pulmonary valve stenosis. Seven patients had a patent ductus arteriosus (PDA). In two neonates the pulmonary valve could not initially be crossed, but was crossed and successfully dilated at a later date after a sys-

temic pulmonary shunt had been placed. One patient with a right ventricular pressure of 268 mm Hg and without a PDA developed hypotension and bradycardia when the pulmonary valve was crossed during the diagnostic study, and subsequently died after an emergency systemic pulmonary shunt. The right ventricular pulmonary systolic pressure gradients fell from 87 (8) mm Hg before PBV to 19 (3.2) mm Hg after PBV at 8.6 (2.2) months of follow up ($p < 0.0001$). Only one patient required repeat PBV.

PBV is an effective treatment for critical pulmonary stenosis in neonates and infants: caution is advised, however, in patients without a PDA.

Presentation of ventricular tachycardia in children

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Twenty children were referred with ventricular tachycardia (VT) between 1978 and 1988; mean age was 4.5 years (range: birth–15.3 years), and the sex ratio was equal. Heart failure was the presenting feature in five (25%), mean age 7 months (range: birth–1.5 years). VT followed a viral illness in two and one child had a cardiomyopathy. Five (25%) presented with syncope, mean age 9.6 years (range: 6–15.3 years). One child had a long Q-T syndrome (LQTS), and one a cardiomyopathy. In two, syncopal attacks had been mistaken for epilepsy. Tachycardia during viral illness was the presenting feature in two (10%), aged 13 and 18 months. Two (10%) presented with palpitations aged 6.2 and 7 years. The finding of an irregular pulse first brought four symptom free children (20%) to medical attention, mean age 5.3 years (range: birth–13.8 years). VT was later shown on Holter monitoring. In one child this followed a viral illness and one child had a VSD. Torsade de pointe VT occurred in two children (10%) aged 3 months and 2.3 years, respectively, both with a LQTS. One occurred during routine Holter monitoring and one postoperatively (Fallot's tetralogy and pacemaker). VT was initially mistaken for a supraventricular tachycardia in seven (35%). Five of these had narrow complex His bundle VT, mean age 8 months (range: birth–1.5 years). Six received inappropriate initial antiarrhythmic drugs resulting in cardiac arrest in three.

In conclusion, VT in children may be asymptomatic or present as a life threatening arrhythmia. Initial presentation and ECG may lead to difficulties in diagnosis and management.

Early coronary atherogenesis and myocardial infarction in Asians: a problem of glucose metabolism

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Ethnic differences in 128 consecutive male patients presenting with first myocardial infarction (MI) were examined. Infarction rates were derived using data from the 1981 census. Coronary arteriograms on 99 survivors were scored by two 'blinded' observers. Six months after the MI cholesterol (TC), triglycerides (TG), HDL cholesterol (HDL), and glucose (BS) were measured from a single oral glucose blood sample. Age and race matched controls were recruited for identical blood tests. Rates of MI were significantly (three times) higher in Asians in all age groups. Plaque numbers were greater in Asians (3.96 (2.27) *v* 2.04 (1.65)) than in whites ($p < 0.001$). In the patient groups 34% of Asians *v* 13% whites ($p < 0.005$) had diabetes or impaired glucose tolerance (IGT). Cholesterol in whites was 6.18 (1.05) *v* 5.56 (0.94) Asians ($p < 0.002$). TGs in Asians were 1.96 (1.06) *v* 1.56 (0.76) ($p < 0.05$). HDL was lower in Asians (0.88 (0.24) *v* 1.09 (0.24) ($p < 0.001$)). In controls 30% of Asians *v* 8.8% whites ($p < 0.01$) had diabetes or IGT. Cholesterol was higher in Asians (5.56 (0.99) *v* 5.07 (0.86) in whites ($p < 0.05$)). TGs were 1.32 (0.70) in Asians *v* 1.25 (0.69) in whites $p = \text{NS}$. HDLs were 1.09 (0.34) in Asians *v* 1.19 (0.20) in whites ($p = \text{NS}$).

We conclude that rates of IGT and diabetes are higher in Asians than whites but not greater in Asians with MI than controls. Unfavourable lipid profiles with high TGs and low HDL were present in Asians with myocardial infarction. These data suggest that in Asians, adverse TGs and HDL concentrations are associated with MI but diabetes is not.

Comparative lack of free radical generation by the myocardium during cardiac surgery

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Diffuse impairment of ventricular function after cardiac surgery may be associated with the generation of oxygen derived free radicals during reperfusion of the myocardium. Ten patients undergoing elective coronary bypass surgery were studied using a pre-

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viously described assay of peroxidised lipids as an index of free radical activity. Blood samples were obtained from systemic arterial, mixed venous, and coronary sinus catheters, and the ratio of octadeca-9, 11-dienic acid to linoleic acid was measured in the plasma phospholipid and free fatty acid fractions by high performance liquid chromatography.

The 10 patients were men aged 49 to 67 years with good preoperative LV function (angiographic LVEF $\geq 55\%$). All underwent coronary surgery on cardiopulmonary bypass with a membrane oxygenator, relative hypothermia 30°–34°C, and intermittent cross clamping of the aorta. During the ischaemic periods there were no changes; during the reperfusion phase there was a significant rise in peroxidised lipid ratio in the free fatty acid fraction in arterial and in mixed venous blood, but not in coronary sinus blood (arterial 3.60 (1.17) to 3.82 (1.13), $p < 0.05$; mixed venous 3.49 (1.17) to 3.97 (1.11), $p < 0.05$; coronary sinus 3.84 (0.96) to 3.87 (1.18), $p = \text{NS}$). There were no significant changes in the phospholipid fraction throughout the study period.

These data suggest that much of the observed rise in peroxidised lipids originates from tissues other than the myocardium. Caution will be needed in interpreting such measurements with regard to cardiac events unless samples are obtained specifically from the coronary sinus, as well as from systemic sites.

Influence of platelets on extent on myocardial infarction during coronary artery occlusion

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We have previously shown that platelet activation may contribute to the haemodynamic and arrhythmogenic effects after early coronary artery occlusion (CAO). To investigate the possible influence of platelets on the rate of myocardial necrosis, we measured extent of infarction following 30 minutes obtuse marginal CAO in the rabbit. Four sections of equal thickness from base to apex were obtained and after staining with nitroblue tetrazolium necrosed tissue was measured by planimetry. Results were calculated as the volume of myocardium infarcted and then expressed as % of the zone at risk. The zone at risk, obtained for each of the four sections from base to apex in five hearts after 90 minutes CAO, was 44%, 47%, 60%, and 80% (or 53% of the total myocardium at risk). After 30 minute CAO in 10

controls, SAP decreased by 27% ($p < 0.005$), while heart rate remained unchanged and five developed VF. The extent of infarction (as % zone at risk) was 53%, 46%, 38%, and 31% from base to apex (or 43% of the total myocardium). Antiplatelet serum (APS, 1 ml/kg given intravenously before CAO) decreased platelet count by 98% ($n = 9$) and SAP decreased by 6% (NS); heart rate was unchanged and only two developed VF. The extent of infarction was 28%, 31%, 37%, and 21% of the zone at risk (29.5% of the total). Thus in the presence of platelet depletion there is a marked reduction in the rate of development of myocardial infarction especially in the basal region.

These findings indicate that platelet activation may contribute to the rate of necrosis in the early stages of acute myocardial infarction.

The role of echocardiography and Doppler and colour flow mapping before, during, and after dilatation of the mitral valve.

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Eighty seven cross sectional echocardiographic and Doppler and colour flow mapping studies in 24 patients undergoing dilatation of the mitral valve have been critically evaluated. Echocardiographic factors predictive of successful outcome included good main leaflet body mobility, lack of significant subvalvar calcification, and left atrial diameter < 6.5 cm. Contraindications were left heart thrombus or valvar regurgitation $>$ grade 2. Assessment of the valve area by planimetry, leaflet mobility, calcification, Doppler maximum and mean pressure gradients, Doppler valve area (by pressure half time), and colour flow characterisation of left ventricular filling pattern were performed before, three days, three, six, and 12 months after the procedure. Mean echo/Doppler valve area increased from 1.11 cm^2 to 1.67 cm^2 . Colour flow mapping showed increase in mitral regurgitation by one grade in three cases, transient small atrial septal defect in two, and complex dual left ventricular filling patterns in three where isolated medial or lateral commissure separation was seen on cross sectional echocardiography. Echocardiography and Doppler and colour flow mapping was performed during the procedure in nine patients and this monitored any increase in regurgitation, LV filling during inflation, and bal-

loon position. In three cases pericardial effusion was detected and aspirated using echo guidance.

In conclusion, echocardiography and Doppler and colour flow mapping have an essential role in the selection of patients for dilatation of the mitral valve, intraprocedure monitoring, and long term follow up.

Clinical outcome and procedural risks of complete compared with incomplete revascularisation by percutaneous transluminal coronary angioplasty in patients with multivessel disease

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Coronary angioplasty (PTCA) is being increasingly performed in patients with multivessel disease (MVD) and emphasis is given to completeness of revascularisation to improve clinical outcome, although this is not always possible. We have retrospectively reviewed the clinical outcome in 86 patients with MVD who underwent PTCA in our centre between January 1985 and June 1988. Complete revascularisation was achieved in 29 patients (group I) and incomplete revascularisation in 50. Of the 50, complete revascularisation had been intended at the outset in 18, but only incomplete revascularisation could be achieved for technical reasons (group IIa). The remaining 32 patients had a planned incomplete revascularisation as it was felt that the non-dilated vessel supplied a smaller area of viable myocardium (group IIb). Over a mean follow up period of 16 (10) months, 21 (72%) in group I, 12 (67%) in group IIa, and 26 (81%) in group IIb, remained symptom free or greatly improved. Three (10%) in group I, 2 (11%) in group IIa, and 2 (6%) in group IIb, had to undergo CABG. PTCA was repeated in four patients in group I, none in group IIa, and one in group IIb. One patient died after an MI in group I. There were no deaths in group IIa or group IIb. None of these differences was significant. Forty nine patients had PTCA to one vessel alone in the presence of MVD; a major procedure related complication (MI/CABG) occurred in two (4%) and there no deaths. The remaining 37 had PTCA to more than one vessel. Two patients (5.5%) suffered a major complication in this subgroup, and there were two (5.5%) procedural deaths ($p < 0.05$).

We conclude that in selected patients, incomplete revascularisation can be associated with a high incidence of clinical improvement and low subsequent cardiovascular event rate at follow up. The risk of the

procedure is related to the number of vessels dilated and is not increased as a result of incomplete revascularisation. Thus single vessel PTCA aimed at incomplete revascularisation should be given serious consideration in patients with MVD.

Epidemiological features of the idiopathic cardiomyopathies: a population based study

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Previous estimates of the incidence and prevalence of idiopathic dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) have been based primarily on data from tertiary referral centres, hospital discharge statistics, or necropsy series. Such data are unlikely to reflect accurately the occurrence of disease in the general population. The purpose of this study was to document the incidence and prevalence of DCM and HCM in the population of Olmsted County, Minnesota, for the years 1975–1984. Using the Mayo Clinic records linkage system, which accesses diagnostic data on the entire population of Olmsted County, we identified 45 new cases of DCM and 19 new cases of HCM during the 10 year period. Age and sex adjusted incidence rates were 6/100 000 person-years (p-y) and 2.5/100 000 p-y, respectively. The incidence of DCM increased from 3.9/100 000 p-y in the first five years to 7.9/100 000 p-y in the last five years of the study. The corresponding change for HCM was from 1.4 to 3.6/100 000 p-y. Age and sex adjusted prevalence rates of DCM and HCM were 38/100 000 and 20/100 000 population, respectively. Of the prevalent DCM cases, 48% (14/29) were <55 years on prevalence day (1 January 1985). Almost half of these (6/14) were NYHA functional class III or IV at diagnosis. Thus the prevalence of advanced myocardial disease due to DCM in persons <55 years was 7/100 000 population.

This unique population based study provides the most accurate epidemiological data currently available on the occurrence of DCM and HCM. The estimates derived may be useful for health care planning, particularly for the development of cardiac transplantation facilities.

Cardiac abnormalities in systemic lupus erythematosus: association with raised cardiolipin antibodies

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A thrombotic tendency in systemic lupus erythematosus (SLE) has been associated with raised cardiolipin antibodies (CA). We studied 34 consecutive patients with SLE to find out whether these patients also have an increased incidence of cardiac abnormalities by complete echocardiographic and colour flow Doppler examination. The CA state of the patients was not known at the time of the ultrasound studies. The patients ages ranged from 16 to 64 years (mean 35.5). Fourteen (41%) of the patients had raised titres of CA. Thirteen (93%) of these had at least one cardiac abnormality. Eleven had abnormal valves (valvar thickening in two, regurgitation in five, and Libman-Sacks vegetations in four). Two patients had partial or global myocardial dysfunction, one of whom also had a small pericardial effusion. Only one patient with raised CA had an echocardiographically normal heart, and this patient had recurrent venous thromboses. In contrast none of the 20 patients with normal CA titres showed structural valvar disease although two had small pericardial effusions.

It is concluded that a raised CA is an indicator of probable cardiac impairment in SLE. This knowledge may be important in guiding decisions about treatment.

Exercise renography in patients with heart failure

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Renal blood flow is impaired in patients with heart failure, especially during exercise. This is difficult to evaluate using standard clearance methods. The radioisotope renogram has therefore been studied at rest and during incremental exercise to examine its role in the assessment of renal perfusion. Rest ($n = 22$) and exercise ($n = 26$) renograms were performed on 18 patients using 123-I orthohippurate. Renal counts were recorded for 30 minutes. Freewheel exercise using a bicycle ergometer was performed for the first three minutes. Thereafter the work was increased in 25 Watt steps every three minutes until the limit of work capacity. Radionuclide injection coincided with the start of exercise. The mean fractional shortening was 23 (11)%. Most renograms done at rest were normal. Exercise renograms were of normal pattern in patients in NYHA class I ($n = 5$). There was a flattening of the washout phase in the

renograms in class II ($n = 8$) which occurred earlier in class III ($n = 5$). The time at which the flattening started was defined as the threshold time. In patients in classes I, II, and III it was 12.8 (2.5), 5.8 (2.4), and 2.1 (0.9), (mean (SD)), respectively ($p < 0.001$).

These studies show that the changes in the renogram during exercise are associated with the severity of failure and reflect the change in blood flow due to exercise. A second peak occurred in the renogram after exercise in 12 patients that was indicative of reactive hyperaemia occurring after the renal vasoconstriction caused by exercise.

Neuroendocrine responses to captopril in acute heart failure after myocardial infarction

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Angiotensin converting enzyme inhibitors may have diverse neuroendocrine effects in heart failure. We measured atrial natriuretic peptide, angiotensin II, and noradrenaline in 20 patients with heart failure complicating myocardial infarction, and after incremental doses of captopril at hourly intervals to reduce pulmonary occluded pressure (POP) to < 16 mm Hg or to a total dose of 25 mg. Plasma angiotensin II (AII), atrial natriuretic peptide (ANP), arginine vasopressin (VAP), and noradrenaline (NA) were raised at 51 (21) pmol/l, 185 (25) pg/ml, 9.6 pg/ml, and 7.1 nmol/l, respectively. ANP correlated both with right atrial pressure (RAP) and pulmonary occluded pressure, both $r = 0.5$, $p < 0.05$, while AII correlated with POP, $r = 0.4$, but not with systemic vascular resistance (SVR). After captopril, AII fell to 6.8 (1.7) pmol, $p < 0.001$, with accompanying fall in POP from 25.7 (1.9) to 19.3 (1.4) mm Hg, and SVR from 1608 (83) to 1345 (52) dyn cm^5 . Plasma NA and AVP were unchanged at 7.1 (2.2) nmol/l and 7.9 (2.2) pg/ml, respectively. Despite RAP falling from 11.1 (0.8) to 8.7 (0.7) mm Hg, $p < 0.001$, ANP remained unchanged at 209 (22) pg/ml, being no longer correlated with either RAP or POP.

Thus the neuroendocrine and haemodynamic responses following captopril are complex. The persistent rise in ANP despite falls in RAP and POP suggest an additional beneficial mechanism of captopril in ameliorating heart failure by promoting natriuresis.

The effect of loading conditions on the right ventricular pressure-volume association

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In order to characterise the effect of loading conditions on the right ventricular pressure volume association (RVPVR), calibrated biplane ventriculograms with simultaneous microtip pressure measurements were obtained from 16 patients with RV pressure load (RV systolic pressure 58 (9) mm Hg—group 1), five with RV volume load alone (RV systolic pressure 30 (6) mm Hg—group 2), and 10 after relief of RV pressure load (RV systolic pressure 28 (7) mm Hg—group 3). Left ventriculograms were obtained in a further three patients after the Mustard operation (where the left ventricle is the pulmonary ventricle). Pressure volume loops were constructed and compared with our previously published normal data. When compared to the more triangular normal RVPVR, loops obtained in group 1 were square or rectangular with little ejection occurring during pressure decline ($p < 0.001$). Indeed, they more closely resembled those described for the normal left ventricle. The shape of the loops obtained from patients in groups 2 and 3 were not significantly different from normal although end diastolic volume was increased in both. Interestingly, left ventricular pressure volume loops obtained after the Mustard operation were also indistinguishable from those of the normal RV, suggesting that the changes observed are independent of ventricular morphology.

In conclusion, the shape of the normal RVPVR reflects a series of load dependent phenomena. This may have important implications when attempting to measure right ventricular function.

Diagnosis of left ventricular pseudoaneurysm by colour Doppler flow mapping

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Left ventricular pseudoaneurysm (LVPA) is defined as a cardiac rupture contained by adherent pericardium. It is an unusual complication of myocardial infarction, cardiac surgery, and chest trauma. Due to the tendency of LVPAs to rupture, early recognition is of paramount importance, as surgical repair may be curative. Eleven consecutive patients with cardiac

rupture forming left ventricular pseudoaneurysms (LPVA) have been studied using colour flow mapping (CFM), five with acute rupture following myocardial infarction, two following stab wounds, one late rupture of a calcified "true LV aneurysm", one post surgical resection of an LV aneurysm and two resulting from LV venting. Recurrent rupture following repair of LPVA occurred in two patients. The study group therefore comprised 13 cases. The diagnosis was suspected clinically in only 6. Cross sectional echocardiography alone confirmed the diagnosis in 7/13. In all 13, CFM findings were compared with angiographic and surgical information. In all 13 CFM showed flow in and out of the pericardial cavity at the defect site as well as the abnormal flow pattern within the pseudoaneurysm. Pulsed Doppler at the defect site revealed a consistent multiphasic "to and fro" flow pattern the peak velocity of which showed a characteristic respiratory variation. This intracardiac flow pattern is diagnostic of a pseudoaneurysm.

We conclude that in view of the above findings duplex scanning with integrated CFM is the diagnostic technique of choice of cardiac rupture.

Growth potential of the immature transplanted rat lung

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In heart lung transplantation in young children the potential for lung growth is uncertain. Thus unilateral left lung transplantation was carried out on immature rats (<6 weeks of age, when alveolar multiplication is incomplete). Isogenic (Lewis) and non-isogenic immunosuppressed (BN to Lewis) transplants were made, four in each group. All were killed six months postoperatively. Right and left lungs were analysed separately using light microscopic quantitative techniques, and the findings were compared with controls matched for age and strain. Body and heart weight was normal in all. The left lung was normal in volume, with alveoli of normal size and number in non-isogenic rats. Lung volume was abnormally large ($p < 0.005$) in isogenic rats because of an increase in alveolar size ($p < 0.05$), alveolar number being normal. The right lung of both non-isogenic and isogenic rats showed an increase in lung volume and alveolar number ($p < 0.01$ for both). In addition, hilar stripping of the left lung (without transplantation) in Lewis rats of

the same age ($n = 4$) showed that denervation alone did not affect left lung growth but led to a lesser but significant increase in right lung volume ($p < 0.005$) due to a non-significant rise in alveolar size.

Thus after transplantation alveoli continued to form to achieve a normal number and normal lung volume, despite the non-isogenic rats being immunosuppressed and showing evidence of low grade rejection activity. The hypertrophy of the contralateral lung seen in this model of unilateral transplantation was only partly attributable to denervation.

Coronary artery ectasia: prevalence, frequency of hyperlipidaemia, and influence on myocardial perfusion

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During a 12 month period 452 consecutive patients underwent coronary angiography for suspected coronary artery disease (CAD). Of these, 395 were abnormal and 18 (4.5%) showed either localised or diffuse coronary artery ectasia (CAE). All male patients below 60 years of age had their serum lipids and lipoproteins measured immediately before cardiac catheterisation. Their total number was 178 which included 10 patients with CAE. The mean value for total cholesterol (TC), triglyceride (TG), and low density lipoprotein cholesterol (LDL-C) in the CAE patients was no higher than in those with non-ectatic CAD, but the ratio of HDL-C:LDL-C was significantly lower (0.18:0.22, $p = 0.05$). Eight of the 10 patients with CAE were found to have TC, TG or LDL-C above age related 95th percentiles, or HDL-C below the 5th percentile of control subjects, compared with 80 of 168 (48%) of non-ectatic CAD patients ($p = 0.05$). In four of those with ectasia the only lipid abnormality was a low HDL-C (hypolipoproteinaemia). Three patients were found to have non-obstructed ectatic vessels and underwent exercise stress testing with cross sectional echocardiography and thallium radionuclide scanning. Objective evidence of myocardial ischaemia in regions supplied by non-obstructed ectatic vessels was documented in two of these patients, both having a positive thallium scan, with one developing diagnostic ECG changes, and reversible regional wall motion abnormality on echocardiography.

In summary these findings show that serum lipid and lipoprotein abnormalities are common in CAE patients. This suggests that an imbalance between these lipoproteins may play a pathogenetic role in this uncommon form of coronary arteriopathy. Non-obstructed ectatic arteries may also be a substrate for exercise induced myocardial ischaemia.

Transcardiac changes in platelet function before and after angioplasty

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While not proved, restenosis after angioplasty is thought to be by proliferation of arterial wall smooth muscle cells, perhaps stimulated by the interaction between activated platelets and the balloon damaged vessel wall. To determine whether platelets are activated by coronary angioplasty we have assessed transcardiac changes in platelet function with aggregometry, and transcardiac platelet granule release by measuring β -thromboglobulin (BTG) before and after angioplasty. Samples of blood were taken from the aortic root and coronary sinus before dilatation (A1 and C1 respectively) and from the same sites (A2 and C2) within five minutes of the completed procedure, in a total of 21 patients. The platelet activation index, a sensitive measure of platelet hyperaggregability, was significantly higher in C2 (mean 9.4; 95% confidence interval 7.5 to 11.3, than in A1 (6.2, 4.8 to 7.7), ($p = 0.014$), A2(7.1, 6.4 to 7.8), ($p = 0.039$) or C1 (6.5, 5.7 to 7.3) ($p = 0.013$). Levels of BTG were higher in C2 (median 5.1 ng/ml; interquartile range 4.0-6.3) than A2(4.4 ng/ml, 3.3 to 5.7) and C1 (4.9 ng/ml, 3.5 to 5.8), but only reached significance when compared with A1 (4.3 ng/ml, 3.1 to 5.4) ($p < 0.05$).

Our data have shown that coronary angioplasty has a significant effect on platelet function. If angioplasty induced platelet aggregation could be pharmacologically prevented, subsequent restenosis might be reduced.

Collateral vessels after infarction: association with left ventricular damage and coronary disease, and influence on exercise testing and clinical outcome

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Associations between collateral vessels, left ventricular (LV) damage, and coronary artery (CA) disease, and their influence on submaximal exercise testing (SMET) and outcome after myocardial infarction (MI) are unclear. Of 302 consecutive survivors of MI, 262 underwent an early SMET. Of 139 patients with abnormal tests, 123 underwent cardiac angiography; extent of LV damage, CA disease, and collaterals to the infarct territory were scored. Extent of LV damage was not associated with the extent of CA disease or collateralisation but extent of collaterals was significantly related to extent of CA disease. Odds of dying in the first year following MI or suffering a further ischaemic event were doubled by an LV score ≥ 21 and a CA score ≥ 19 , respectively. Collaterals did not influence outcome. Features of the SMET significantly associated with LV damage included lack of ST depression, but prolonged ECG recovery time if it occurred, an abnormal blood pressure response, and ST segment rises. Features associated with extent of CA disease included degree of ST segment depression, stage when it first occurred, its presence in the infarct territory, ECG recovery time, and lack of ST segment elevation or ventricular arrhythmias. Multivariate analysis identified independent predictors of these variables: (a) LV score ≥ 21 —lack of ST depression, ECG recovery time > 2 mins, and ST elevation, and (b) CA score ≥ 19 —ST depression ≥ 3 mV. Major collaterals were more likely with ST segment depression, a greater degree of ST depression, and absence of ventricular arrhythmias.

We conclude that SMET variables are useful predictors of the extent of LV damage and CA disease after infarction; the extent of collaterals, which can be predicted by SMET variables, is associated with the extent of CA disease but not with clinical outcome.

Comparative value of clinical and electrophysiological variables in the prediction of arrhythmic events after myocardial infarction

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The value of a number of different variables in the prediction of arrhythmic events was assessed in a series of 75 postinfarction patients. Late potentials (LP) were detected using Simson's method; ventricular stimulation was performed using the Wellens protocol; exercise testing was performed using a

modified Bruce protocol, and ejection fraction was determined using either gated blood pool scan or cineventriculography. The mean age of the patients was 56 years, median 55; 13% had had previous infarctions. All tests were completed within six weeks of infarction. During a mean of 18 (median 10) months follow up, six patients developed symptomatic ventricular tachycardia (VT); there were no sudden deaths. Multivariate analysis showed that the single most important predictor of arrhythmic events was inducible, sustained, monomorphic VT (sensitivity 6/6(100%)), positive predictive accuracy (PPA) 6/8(75%). Induction of repetitive ventricular responses, non-sustained VT and polymorphic VT or ventricular fibrillation, were poorly correlated with the occurrence of arrhythmic events. Clinical criteria were sensitive but inaccurate predictors of arrhythmic events (occurrence of in hospital complications, sensitivity 5/6(83%), PPA 5/27(19%); ejection fraction, sensitivity 4/6(67%), PPA 4/18(22%)); LP or an ectopic frequency of ≥ 10 /hour were sensitive (5/6(83%), and 4/6(67%)) but also inaccurate predictors of arrhythmic events (PPA 5/20(25%), and 4/13(31%)). The exercise test was of little value in predicting arrhythmic events (PPA 2/42(5%)), but was positive in all three patients who reinfarcted. Combinations of the non-invasive tests did provide increased accuracy (for example, LP + tape, PPA 4/6(67%)) but no combination was as sensitive or as accurate as inducible, sustained monomorphic VT.

In conclusion, inducible sustained, monomorphic VT is a sensitive and accurate predictor of arrhythmic events after myocardial infarction; clinical data and non-invasive electrophysiological tests are also sensitive but comparatively non-specific prognostic indicators.

Angioplasty of bifurcation lesions in major coronary vessels

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Coronary stenoses affecting a bifurcation have previously been considered unsuitable for balloon dilatation when occlusion of a major vessel may occur in 30% of cases. Using techniques specifically tailored to lesion morphology, successful angioplasty was performed in 26 patients with lesions affecting the origin of a large branch vessel. The lesions were in the anterior descending/diagonal in 20, the circumflex/obtuse marginal in five, and the posterior

descending/posterolateral in one. Simultaneous dilatation with two balloons was performed in eight patients. In four cases two guide catheters were used, a single guide catheter being used in the remaining four. In this group 2.5 mm balloons were used in three cases and a balloon probe with a 3 mm mono-rail in the remaining case. In 18 patients important compromised branch vessels were protected by a second guide wire. In these patients successful angioplasty of the bifurcation was achieved but unplanned dilatation was required in three patients to correct iatrogenic stenosis in a previously unstenosed vessel. Primary success was achieved in all with no major complication. Serious disruption of the vessel proximal to the bifurcation was seen in three patients. In seven patients, however, lesions recurred within six months in one or both limbs and were successfully redilated in two.

Successful angioplasty of complex lesions can be achieved if attention is paid to lesion morphology and choice of technique.

Epicardial electrogram during successive balloon occlusion during percutaneous transluminal coronary angioplasty

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We have recorded an electrogram from the guide-wire during percutaneous transluminal coronary angioplasty (PTCA) monophasic action potentials from the right ventricular septum, and an ECG, with a view to a qualitative assessment of the procedure. We have studied 20 patients undergoing PTCA for lesions in the left anterior descending ($n = 12$) circumflex ($n = 3$) and right coronary artery ($n = 5$). Measurable changes in the electrogram were obtained only from the left system. Of these 15 patients two showed no ST segment change during the procedure. The remaining 11 patients registered up to 5.4 mm of ST elevation in the electrogram with the deflated balloon in position across the stenosis (mean (SD) 1.8 (1.6) mm. During balloon occlusion ST elevation was present up to 7 mm in 14 of the 15 patients (3.0 (1.9) mm. On deflation the electrogram registered either reduction, no change, or an increase in ST elevation compared with the previous control value. After successive inflations and deflations a final reduction of the initial control ST use of more than 50% was associated with a good angiographic result, whereas a fall of less than 50% or an increase above the control value was associated with only a moderate result. Although we were able to record

from the right coronary artery the signals were of low amplitude and registered only minimal ST and T changes, probably due to cancellation. There was no obvious correlation between angiographic evidence of collateral supply with either the changes in ST rise between inflations or the magnitude of ST elevation during inflation. In the 17 patients undergoing PTCA of the right and left anterior descending coronary artery, ischaemic changes in MAP duration were only registered in two (despite positioning the MAP electrode in the area normally supplied by the vessel) because of the extremely local nature of the 60 second ischaemic intervention. As would therefore be expected the electrocardiogram was less sensitive than the electrogram, ST changes often being minimal or absent and they did not provide useful sequential data.

Our results show that assessment of ST segment changes in the electrogram recorded from the PTCA guidewire during periods of balloon deflation between successive occlusions provide evidence of a good angiographic result when any initial ST elevation had subsequently been reduced by 50% at the end of the procedure. There was no correlation with angiographic evidence of collateralisation.

Dynamic angioplasty in normal and abnormal coronary arteries

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The "Kensey" catheter is a new device for treatment of occlusive vascular disease. We have successfully used an 8 F device in peripheral arteries. We used a 1.8 mm resolution angioscope to study the effects of an experimental 5 F Kensey catheter in normal pig and necropsy human coronary arteries. In 23 normal porcine arteries small intimal flaps were produced in 21 arteries. This occurred independent of tip rotation speed (20–80 000 rpm). These intimal flaps were usually single and small (<25% of the lumen). The catheter was seen to keep a central position in the arterial lumen when fluid was injected, resulting in only one perforation. In 25 normal porcine arteries the catheter was forced through single narrowings created by band ligation. The perforation rate increased with cam speed (0% at 20 000 rpm, 16% at 40 000 rpm, and 29% at 80 000 rpm, respectively). Perforations were rarely diagnosed angioscopically, the common findings being of large multiple obstructive intimal flaps. In seven necropsy human coronary arteries angiography was more sensitive than angiography in detecting the aetiology of occlusion (thrombus *v* atheroma). It also detected dissections

that were missed on angiography. Kensey atherectomy was performed on all seven arteries successfully reopening stenotic and occluded arteries with one perforation.

We conclude that (a) angioscopy is a sensitive method of detecting minimal vessel damage and (b) that the Kensey catheter has applications in the coronary artery, but that the approach should be cautious.

Comparison of visual estimation, measurement by hand held callipers, automated digital quantification, for the assessment of results of percutaneous transluminal coronary angioplasty

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Digital subtraction coronary angiograms of 27 patients who underwent coronary angioplasty to a total of 32 lesions were analysed using an automated border detecting computer program and hand held calliper measurement of diameter percent stenosis. The results were compared with visual interpretation of the 35 mm cineangiograms. Visual reports significantly overestimated the pre PTCA diameter percent stenosis ($p < 0.001$) and underestimated the residual post PTCA narrowing when compared with the automatic computer program ($p < 0.001$). Calliper measurements significantly overestimated the pre PTCA stenosis in comparison with the computer ($p < 0.01$), but post PTCA the two methods did not differ significantly ($p = 0.105$). There was a positive but poor correlation between callipers and computer measurements ($r = 0.43$, $p < 0.05$) performed on the pre PTCA digital angiograms. Post PTCA the two methods correlated better ($r = 0.78$, $p < 0.001$) but further statistical analysis showed important discrepancies between them. The correlation between visual reports and computer measurements was poor before PTCA (Kendall's $\tau = 0.32$, $p < 0.05$), and not statistically significant after PTCA ($\tau = 0.64$, $p = 0.5$).

We conclude that there is observer bias in the visual reporting of angioplasty results such that pre PTCA lesions are overestimated whereas post PTCA are underestimated. Measurement by hand held callipers improves the assessment of coronary stenoses in comparison with the visual report, but still may not altogether eliminate observer bias, overestimating the pre PTCA stenoses compared with automated border detection.

Percutaneous angioscopy

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Percutaneous angioscopy has been limited in its applications because of poor optical resolution and difficulty in obtaining a bloodless field. We have developed a method of angioscopy that produces high optical quality imaging. Four arteries in three patients were viewed angioscopically using a high resolution Olympus 1.8 mm endoscope attached to a microchip video camera, with a xenon light source. The angioscope and video camera were sterilised in ethylene oxide, and the angioscope inserted percutaneously through an 8 F valved sheath into the artery. Sheaths of various length were used so that the angioscope could be positioned within the sheath close to the area to be inspected. The sheath was flushed with saline above arterial pressure. The angioscopic findings were compared with angiography performed before and after angioscopy. Angioscopy was able to distinguish between stenotic and occlusive disease, thrombus, and atheroma, and detected abnormalities not seen on angiography, including intimal flaps, fractured atheromatous plaque, and fresh thrombus in two of four introducer sheaths despite the patients having had large doses of heparin. In three of these arteries dynamic angioplasty was performed; angioscopy was again able to detect intimal damage and loose atheroma fragments not seen on angiography. The amount of flush solution used in each case was high (average 1.3 litres).

Our patients were assessed carefully before and after angioscopy and none developed signs of fluid overload; further techniques to reduce the flush volume are needed, however, before this valuable technique can have a wider clinical application.

Laser thermal angioplasty: limitations in the coronary circulation

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To identify the factors responsible for the poor primary success rate of metal-capped optical fibres in the coronary circulation we performed the following experimental studies using an argon laser coupled to a 2.0 mm metal capped optical fibre. (a) The histo-

logical effects of laser were studied at 115 intra-coronary sites in 12 cadaver hearts during aortic perfusion with either saline or blood. Endothelial thermoablation occurred at 76(23)J, and 47(22)J, respectively, ($p < 0.05$) and perforation at 156(24)J, and 66(25)J, ($p < 0.001$). Significant thermal damage to the contralateral normal arterial wall was a consistent feature in the presence of eccentric plaque, suggesting a less favourable outcome when this geometry exists. Furthermore, at energies required for thermoablation, adherence of the metal cap to the arterial wall resulted in trauma ranging from intraluminal flap formation to arterial intussusception. (b) The thromboembolic risk was assessed in an in vitro circuit during perfusion with 10 ml aliquots of blood at either 5 or 40 ml/minute during delivery of laser pulses of increasing power (4, 8, and 12 W) and time (3, 6 and 9 seconds). Nine aliquots were laser treated at each of the nine possible combinations of power and time; a tenth served as control. The effluent was filtered through five in-line filters to assess debris formation. Higher blood flow resulted in significant debris formation compared to controls at all combinations of power and time. At lower flow this difference was not significant at 4 W (6(14) μ g) or 8 W for three seconds, but was significant for all remaining energies to a maximum of 198(35) μ g at 12 W for three seconds ($p < 0.001$). Scanning electron microscopy showed fragments > 1 mm. (c) The risk of atheromatous embolism was assessed using a similar circuit incorporating coronary endarterectomy specimens treated with laser in saline. Sixty segments were treated: 10 at each of 4, 8, or 12 W for 10 or 20 seconds. Twenty other segments manipulated in a similar way but without being treated served as controls. Weight loss was greater in treated segments than controls (23(14) mg *v* 5.4(2.3) mg, $p < 0.001$) although calcific foci were resistant. Total debris produced was greater than controls (275(118) μ g *v* 155(65) μ g, $p < 0.005$). Most fragments were < 50 μ m although some of 200–300 μ m were seen.

In conclusion, although atheroma can be debulked, the application of these fibres is limited by arterial adherence, circumferential thermal damage in the presence of eccentric lesions, inability to ablate calcific plaque, and the potential for distal embolism.

Haemodynamic and renal effects of low dose infusions of atrial natriuretic peptide in chronic heart failureJ J Polonia, P Montorsi, G Tonolo, B Leckie, D Northridge, H Dargie, A M Richards
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High dose infusions (> 25 pmol/kg/minute) of atrial natriuretic peptide (ANP) cause a diuresis accompanied by a fall in systemic vascular resistance (SVR) and mean arterial pressure (MAP), but these infusions produce high plasma concentrations of the peptide. In order to elucidate the role of ANP at concentrations found in chronic heart failure we administered a low dose infusion (5 pmol/kg/minute) for four hours to five patients with chronic heart failure (NYHA class III) in a placebo controlled cross over study. Plasma immunoreactive ANP was raised at the start at 113 (24 pg/ml and rose during active infusions to 487 (37) pg/ml. This resulted in a significant rise in urine volume (placebo 2.7(0.6), ANP 4.5(0.9) ml/minute, $p < 0.05$) and fractional sodium excretion (placebo 0.6(0.2)%, ANP 2.9(1.0)%, $p < 0.05$). No significant differences were noted in renal blood flow, glomerular filtration rate, plasma renin activity, plasma angiotensin II, or plasma viscosity. Mean right atrial pressure fell from 9.03(2.3) mm Hg to 6.3(1.2) mm Hg, $p < 0.05$, mean pulmonary artery pressure from 28.2(2.9) mm Hg to 23.2(3.4) mm Hg, $p < 0.05$, and wedge pressure for 16.1(2.6) mm Hg to 13.4(1.8) mm Hg, $p < 0.05$, on placebo compared with ANP, respectively. No effects were noted on cardiac output, SVR, or MAP.

This suggests that low dose infusion of ANP that produces plasma concentrations seen in patients with chronic heart failure, acts primarily on the venous capacitance vessels with no significant effect on SVR. The marked diuretic and natriuretic properties are retained at this lower dose.

Captopril does not potentiate the action of loop diuretics in patients with cardiac failure

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Angiotensin converting enzyme (ACE) inhibitors reduce the plasma concentrations of the sodium retaining hormones angiotensin II and aldosterone. This should lead to an increase in natriuresis and diuresis; placebo controlled studies in heart failure have, however, shown an early weight gain and development of oedema after the introduction of ACE inhibitors. We studied the natriuretic and diuretic response to a 40 mg intravenous dose of frusemide in 12 supine patients with cardiac failure (NYHA III), and repeated these observations on another occasion one hour after a 25 mg oral dose of captopril. Urinary sodium, potassium, and creatinine concentrations were measured for four hours

after the administration of frusemide. Plasma renin activity, angiotensin II, and aldosterone concentrations were measured at hourly intervals. Captopril caused a pronounced reduction in the frusemide induced natriuresis from 120 (9.6) to 67 (11.7) mmol, ($p < 0.05$), urine output also fell from 1166 (60) to 685 (77) ml, ($p < 0.05$). Captopril decreased creatinine clearance from 91 (7.2) to 57 (7.7) ml/minute. Systolic and diastolic blood pressures were 5 and 7% lower after captopril. Plasma renin activity rose from 3.53 (0.76) to 12.34 (4.1) ng/ml and plasma angiotensin II fell from 24.9 (5.05) to 10.72 (2.4) pg/ml with captopril. Plasma aldosterone concentrations were slightly lower with captopril.

ACE inhibitors produce an initial reduction in the supine natriuretic and diuretic responses to a loop diuretic. The dose of diuretics may therefore need to be increased in some patients.

Comparison of the haemodynamic effects of dopexamine and dobutamine in patients with severe heart failure

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Dopexamine is a novel compound with properties of DA_1 dopaminergic and β_2 adrenergic receptor agonism and noradrenaline reuptake inhibition. It has been shown to produce beneficial renal and haemodynamic effects in patients with severe heart failure. A comparative study of its effects with those of dobutamine was performed in nine patients with severe heart failure (NYHA IV). Haemodynamic data were obtained using thermodilution Swan-Ganz catheters and arterial cannulas before and during graded incremental doses of dopexamine (DP) from 0.5 to 6 $\mu\text{g/kg/minute}$ and of dobutamine (DB) from 2.5 to 20 $\mu\text{g/kg/minute}$. The heart rates at basal and at peak infusion rates were similar (DP 87 (17) to 100 (14), DB 91 (18) to 103 (17) per minute), and so were the pulmonary artery occluded pressures (DP 24 (6) to 22 (6), DB 25 (9) to 24 (10) mm Hg), the cardiac indices (DP 1.7 (0.5) to 2.8 (1.1), DB 1.8 (0.5) to 3.0 (1.1) l/minute/ m^2 and the systemic vascular resistances (DP 1553 (221) to 1117 (432), 1721 (347) to 1280 (433) dyn.s. cm^{-5}). The peak left ventricular stroke work index (DP 20 (9), DB 27 (15) g.m/ m^2 , $p < 0.05$) and peak cardiac power output (DP 0.71 (0.36), DB 0.93 (0.46) W, $p < 0.05$) were different.

These data and calculations using an analytical technique of differentiating inotropic from vasodilatory effects showed that dopexamine produced milder positive inotropic effects than dobutamine. Because of the beneficial central haemodynamic effects and its known direct renal vasodilatory property, dopexamine can be considered to be the drug of choice in the short term treatment of the subgroup of patients with heart failure and compromised renal perfusion.

Thrombolytic treatment in cardiogenic shock

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Twenty five patients aged 40–76 (mean 60.8) with acute myocardial infarction complicated by cardiogenic shock were admitted over a two year period. Systolic blood pressure was less than 80 mm Hg despite aggressive inotropic treatment. Onset of symptoms to treatment was less than six hours. Sixteen patients (mean age 56.2) were given 1.5 million units of streptokinase intravenously as well as heparin. Nine patients (mean age 68.8) had conventional treatment without thrombolytic treatment. Delay times to treatment were 132 minutes in the thrombolytic group and 70.5 minutes in the conventional treatment group. All patients had a previous history of ischaemic heart disease. In the streptokinase group, 12 patients (75%) are alive (mean 19.3 months), and four died in hospital. In the conventional treatment group, eight patients died in hospital and one survived for five months after discharge. The observed difference in hospital mortality, despite the small number of cases, is highly significant ($p = 0.003$). Mean time to reperfusion in the streptokinase group was 70.4 minutes. Angiography was performed in only nine patients in the streptokinase group and evidence of reperfusion in the infarct related artery was seen in all.

Cardiogenic shock has a high mortality. Survival after thrombolysis at one year is significantly improved in this condition, thus preserving myocardium and improving morbidity and mortality.

Alcohol and cardiovascular mortality

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A number of studies have shown that both non-drinkers and heavy drinkers have higher total mortality rates than light to moderate drinkers, and some studies show an inverse relation between alcohol intake and cardiovascular mortality. In the British Regional Heart Study of 7735 middle aged British men there have been 504 deaths during 7.5 years follow up. There is a U shaped relationship between alcohol intake and total mortality and an inverse relationship with cardiovascular mortality even after adjustment for established cardiovascular risk factors. The relation between alcohol intake and mortality was examined separately in men with and without recall of cardiovascular or cardiovascular-related doctor diagnoses at screening. The U shaped curve for total mortality and the inverse relationship with cardiovascular mortality were seen only in men with cardiovascular related illness present at initial examination. The data suggest that the U shaped total mortality pattern and the inverse cardiovascular mortality pattern are produced by pre-existing disease, and the movement of men with disease into non-drinking and occasional drinking categories.

The apparent "protection" effect of moderate alcohol intake may be a consequence of this phenomenon and not due to any benefits from alcohol.

The national history of idiopathic dilated cardiomyopathy: a comparison of population based and referred cohorts

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Studies documenting the natural history of idiopathic dilated cardiomyopathy (DCM) report a high annual mortality rate. Since these studies are based on data from tertiary referral centres, however, the observed high mortality may be due to referral bias. We studied survival in a population based cohort of DCM ($n = 41$), identified through the unique Mayo Clinic records linkage system and representing all incident cases of DCM in the population of Olmsted County, Minnesota, for the 10 years 1975–1984. The results were compared with a previously defined cohort of patients referred to the Mayo Clinic with DCM. The median ages at diagnosis in the population based and referred cohorts were 52 and 49 years; sex ratios (M:F) were 3:6 and 1:4, respectively. There was no significant difference between the proportions of the population based and referred cohorts that had cardiomegaly (cardiothoracic ratio on chest x-ray > 0.50), cardiac failure, or electrocardiographic abnormalities at diagnosis or

entry into the study (73% *v* 87%; 93% *v* 80%; and 66% *v* 73%). Survival rates, relative to the United States West North Central population in 1980, were 95% *v* 69% at one year ($p < 0.001$), and 94% *v* 40% at five years, ($p < 0.001$) in the population based and referred cohorts, respectively.

These results suggest that the natural history of unselected DCM is more benign than previously reported and that high mortality in DCM may be a reflection of referral bias.

In vitro flow studies to improve hydrodynamic design of Fontan reconstruction

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After Fontan reconstruction, fluid energy losses in the reshaped paths of flow may critically raise the already raised systemic venous pressure. We performed in vitro flow studies with a view to improving the hydrodynamic design of atriopulmonary connections. Silicone rubber casts of reconstructed heart cavities provided a basis for making models in which a suspension of aluminium dust was used to look at areas of turbulent flow. Smoothing of contours at cavity outflow tracts and 90° junctions was found to reduce turbulence; associated pressure head losses fell from levels equivalent to those of a 50%, to those of a 20%, area stenosis. Pulsation of a valveless cavity in a continuous flow circuit was found to hinder rather than assist net forward flow, turbulence being increased by pulsation. These findings recorded on videotape illustrate the importance of streamlined shaping of anastomotic sites, and show that inclusion of a valveless, contractile chamber, as in a conventional Fontan circulation, may be detrimental in terms of local flow dynamics.

The studies supported our decision to opt for total cavopulmonary connection as an alternative to atriopulmonary connection in 22 children who required Fontan reconstruction. Postoperative angiographic studies shown favourable cavopulmonary flow in these patients.

Venous compared with anatomical repair for double outlet right ventricle with subpulmonary ventricular septal defect

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Thirty patients with double outlet right ventricle and subpulmonary ventricular septal defect, Taussig-Bing disease, who underwent repair over a 14 year period (1973–1987) have been reviewed for their early, intermediate, and long term status. At operation their ages ranged from two months to 8 years (median 12 months) and weight from 3 to 16.5 kg (median 7.5 kg). All 14 patients who had undergone previous palliative operations had pulmonary artery banding and in addition, five of these required repair of a coexisting aortic coarctation, one of an interrupted aortic arch, and one had a Blalock-Hanlon septectomy. Fifteen patients underwent inflow correction of the venous return at atrial level with a Mustard procedure in conjunction with patch repair of the associated ventricular septal defect; in this group there were nine hospital deaths (60.0%). Fifteen patients had anatomical correction, in one patient by an intracardiac repair which was not successful, and in the others by an "arterial switch" Jatene's operation, with two hospital deaths (14.3%). By multivariate analysis, the change over point from the Mustard to the arterial switch procedure was the only event that significantly affected the hospital mortality ($p 0.025$). The 18 survivors have been followed for a period of two months to 148 months (median 23 months). There were two late deaths, both in patients who had repairs by atrial redirection (33.3%). One patient who had the arterial switch operation required closure of a residual ventricular septal defect four months post-operatively. All long term survivors are in functional class I. Postoperative catheterisation in five patients (mean interval 5.8 months) shows normal ventricular function, no valvar regurgitation, and no coronary stenosis.

The improved survival rate, which we expect to continue, together with the satisfactory intermediate functional results have shown that Jatene's operation is the operation of choice for double outlet right ventricle with subpulmonary ventricular defect.

Sinus venosus atrial septal defect: investigation and repair

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Most sinus venosus atrial septal defects (SVASD) are not diagnosed preoperatively, and postoperative atrial arrhythmias are common due to the proximity of the SA node to the site of repair. A review of the

217 ASD repairs performed here in the 10 year period up to March 1988 showed that 57 (26%) were for SVASD. Of the latter, 34 were male and 23 female patients whose ages ranged from 1 to 58 years (mean 14 years). Sixty per cent were symptom free. Echocardiography was performed in 54 patients (95%) but correctly diagnosed the defect in only 4%. Cardiac catheterisation was performed in 35 patients (61%) and was correct in 54%. Overall 38% were correctly diagnosed preoperatively. Operative correction, on cardiopulmonary bypass with hypothermia and cardioplegia, was by pericardial xenograft patch (n = 31), Dacron patch (n = 21), Goretex patch (n = 1), or direct suture (n = 4). Interrupted sutures to hold the patch were placed from outside the heart to avoid the SA node. There was one operative death (1.8% mortality). Follow up ranges from 1 to 96 months (mean 34 months). Two cases were lost to follow up, two patients remain dyspnoeic, and one has a nodal rhythm. The remainder are symptom free and in sinus rhythm.

In conclusion, most SVASDs are still not diagnosed before operation. Because patients are now usually accepted for surgery on echocardiographic evidence alone, the need for careful inspection of cardiac anatomy in theatre is emphasised. The technique of external suture placement may avoid long term rhythm problems.

Total correction of the tetralogy of Fallot: assessment of survival

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During the period from January 1970 to December 1985, 277 patients underwent total correction of the tetralogy of Fallot at two cardiac centres. The mean (SD) age at correction was 7.5 (15.5) years. In 158 patients total repair was performed as a primary procedure whilst 119 previously had a palliative operation (Blalock-Taussig shunt in 72%, Brock procedure in 21%, and Waterston shunt in 7%). A transannular patch was required in 119 cases and 36% of patients received a monocusp homograft patch. The overall hospital mortality was 11.5%. There were only two deaths outside the immediate postoperative period (0-28 days). There was no significant difference in actuarial survival between centres ($\chi^2 = 2.25$, $p > 0.1$), or between primary corrective procedures and staged repairs ($\chi^2 = 0.68$,

$p > 0.1$). Significant differences were found between those patients less than two years at total repair (mortality 18.6%) compared with those older than two years at operation (mortality 8.4%, $p < 0.01$) and between those corrected before 1977 (mortality 15.2%) compared with those repaired during the latter half of the study period (mortality 7.5%, $p < 0.05$). Multivariate analysis of risk of hospital death showed that the independent risk factors were high postoperative RV:LV pressure ratios ($p < 0.001$) and low body surface area ($p < 0.02$). No incremental risk was shown for a transannular patch when a monocusp homograft was incorporated.

In conclusion though hospital mortality from total repair of Fallot's tetralogy has fallen throughout the period of our study, small size at repair and diminutive pulmonary arteries remain important risk factors.

Mustard's operation: long term haemodynamics in symptom free children and balloon dilatation for systemic venous obstruction

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Twenty symptom free children were electively catheterised 10 years after Mustard's operation for simple transposition of the great arteries. Another two patients with signs of superior vena cava (SVC) obstruction were added and underwent balloon dilatation. All patients were anaesthetised and the study was carried out in air and in 100% oxygen. Oxygen consumption was measured with respiratory mass spectrometry and end tidal gases were monitored throughout the study. Mean right ventricular end diastolic pressure was 8.7 (4.6) mm Hg (range: 5 to 20 mm Hg). Two patients had important left ventricular outflow tract obstruction (> 50 mm Hg), and two had minor intracavity obstruction (20 and 25 mm Hg). Cardiac output was normal in 15 and below normal in 5 patients (mean = 3.45 (0.8) l/m²/minute). Pulmonary vascular resistance (PVR) in air of < 3 units was found in 16/19 patients. Gross increase in PVR in air and in 100% oxygen (> 20 units) was present in one patient. Baffle dysfunction was present in 11 patients: 10 with gradients > 5 mm Hg between the SVC or inferior vena cava (IVC) and the systemic venous atrium, and five had a leak identified either by a left to right shunt or by the catheter course. Balloon dilatation was attempted in

eight patients with gradients of >5 mm Hg in the IVC channel, and SVC dilatation was an additional procedure in two of them. Mean gradient was 6.4 (2.3) mm Hg before the dilatation and fell to 4.1 (2.2) mm Hg after the procedure. No pulmonary venous obstruction was identified.

In this selected group of symptom free children, about half had a detectable haemodynamic abnormality. Transvenous balloon dilatation is effective in some patients with systemic venous obstruction.

Heart and heart-lung transplantation in children

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Since August 1984, 76 children aged under 15 years have undergone transplantation. Thirty six patients aged 9 days to 14 (mean 7.5) years underwent heart transplantation (7% of the total population). The main indications were dilated cardiomyopathy in 15 and congenital heart disease (CHD) in five. Forty patients aged 10 weeks to 14 (mean 7.8) years underwent heart-lung transplantation (HLT) (23% of the total) for pulmonary vascular disease, either primary in five or secondary to CHD in 16. Four patients had parenchymal lung disease. There were eight (23%) and 13 (30%) early deaths: moderate pulmonary hypertension in the recipient and bleeding from previous thoracotomy were important risk factors in each group, respectively. With a mean follow-up of 21.6 and 15.4 months, there were one and two late deaths in each group, respectively. To avoid the first risk factor we are now using "primed" hearts from "live" donors. Postoperatively patients were maintained on cyclosporin and azathioprine. Routine steroids are not given. All patients are well, growing normally, and attending normal schools. One patient developed lymphoproliferative disease, which has regressed completely. Two patients after HLT developed obliterative bronchiolitis at 12 and 24 months, and one patient required retransplantation. Routine annual investigations have shown no evidence of chronic rejection in either group.

It is concluded that transplantation offers a chance of remarkable improvement in children with end stage heart and lung disease but long term function, particularly of the lungs, continues to need evaluation.

Decreased pulmonary microvascular permeability in patients with severe mitral stenosis

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In mitral stenosis (MS) a considerable rise in the pulmonary capillary pressure may occur without the development of pulmonary oedema. The mechanism protecting against pulmonary oedema is not known, but might be the result of a reduction in pulmonary microvascular permeability (PMVP). PMVP was measured non-invasively using a previously validated double isotope scintigraphic method that permits calculation of a plasma protein accumulation index (PPA index) for the lung fields. Studies were performed in nine patients with severe MS (Gorlin valve area 1 cm^2 or less, mean pulmonary capillary wedge pressure 27 (4) mm Hg) and in 10 control patients. The PPA index was significantly lower in the MS patients, being 0.17 (0.53) $\times 10^{-3}$ /minute, and 0.46 (0.54) $\times 10^{-3}$ /minute in the control subjects ($p < 0.05$). Furthermore, within the group of patients with MS, there was a correlation between the PPA index and the severity of MS, as reflected by the Gorlin valve area (G): PPA index = 1.35 (G) - 0.67 , $r = 0.7$, $p < 0.05$.

These data indicate that in severe MS, PMVP is significantly reduced, providing a mechanism that protects against pulmonary oedema despite a chronic rise of the pulmonary capillary pressure.

Balloon dilatation of the mitral valve by double and single balloon techniques

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Balloon dilatation of the mitral valve was attempted in 35 patients with symptomatic rheumatic mitral stenosis (mean age 48 years, range 20-80). The valve was successfully dilated in 30 patients. In 20 patients two guide wires were passed through the left heart and stabilised in the descending aorta. This allowed two balloons ($15 \text{ mm} \times 2$ or $25 \text{ mm} + 10 \text{ mm}$ in size) to be inflated simultaneously in the mitral valve. In six patients a bifol balloon ($19 \text{ mm} \times 2$) was positioned on a single wire and in four patients a single balloon (25 mm) was used. The end diastolic mitral

valve gradient was reduced from 14.2 (6.1) to 4.9 (4.2) mm Hg, and mean left atrial pressure fell from 22.6 (6.3) to 13.7 (7.5) mm Hg. The calculated mitral valve area increased from 1.17 (2.9) to 2.28 (3) cm². At cross sectional echocardiography and Doppler assessment within one week of dilatation, the mitral valve area had increased from 1.1 to 1.7 cm². Mitral regurgitation of grade 3/4 developed in one patient who required early mitral valve replacement. Three patients developed tamponade, which was successfully relieved. At follow up (mean 9 months) all patients had improved symptomatically and on repeat echocardiography and Doppler examination the mean mitral valve area was 1.6 cm².

The best results were obtained in the younger patients with mobile valves, but useful improvement was achieved in older patients with calcified valves. The double balloon or bifoil balloon was superior to the single balloon technique. Balloon dilatation of the mitral valve is an effective procedure for the treatment of patients with mitral stenosis and an important alternative to surgery.

Doppler echocardiographic characteristics of prosthetic valves in the tricuspid position

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There is little information available concerning prosthetic tricuspid valve (TV) function. Thirty two patients with prosthetic TV and prosthetic mitral valves (MV) were studied using simultaneous imaging and pulsed wave Doppler echocardiography to measure peak velocity (PkV) m/s and pressure half time (Pt 1/2) m seconds. There were 26 Björk-Shiley and six Carpentier-Edwards xenograft valves in each position. The time from implantation to study ranged from 6 months to 18 years (median 10.5). Twelve native tricuspid and mitral valves were studied as a control group. Doppler data for prosthetic MV and TV flow were obtained in 27 patients with clinically normal valves. Pt 1/2 was significantly longer in the TV 38–197 (median 105.3) mseconds than in the MV, 46–104 (73) msec ($p < 0.02$), but no significant difference in PkV was found, TV 0.6–1.50 (1.02) m/s, and MV 0.40–1.20 (0.91) m/s. There was no correlation between PkV or Pt 1/2 and time since surgery, or valve size. Five patients had clinically abnormal prosthetic TV with: PkV 1.53–1.94 (1.73) m/s, Pt 1/2 237–560 (308) mseconds. Values for the normal TV control group were: PkV 0.34–0.84 (0.54) m/s, Pt 1/2 31–71 (57) mseconds, and for the

normal MV were: PkV 0.40–1.20 (0.91) m/s, Pt 1/2 30–65 (51) mseconds.

Hence data derived from the prosthetic MV cannot be extrapolated to the prosthetic TV. A Pt 1/2 >200 mseconds seems to distinguish important prosthetic TV obstruction from clinically normal prosthetic TV.

Balloon dilatation of the aortic valve: an in vitro assessment of the mechanism, magnitude, and duration of its effects

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Balloon dilatation of the aortic valve (BAV) in adult calcific disease remains a controversial method of treatment with uncertainty as to the magnitude and duration of its effects. We analysed the changes in aortic valve area (AVA) and transvalvular mean systolic gradient (MSG) seen after valvuloplasty in calcified valves removed at operation ($n = 17$) or necropsy ($n = 1$). The intact valves were mounted in a pulsatile flow rig that delivered a constant 4 l/minute saline at 37°C with an ejection period of 45% and pulse rate of 70 per minute. Aortic valve motion was videotaped with a magnifying lens and the AVA then planimetered from the screen. A 20 mm balloon inflated to 3 atm for 30–60 seconds was used for dilatation. The AVA and MSG were measured before, immediately after, and at 5, 10, 20, 30, 60, 120 minutes, 3 days, and 1, 2, and four weeks after dilatation. AVA increased from (mean (SD)) 0.52 (0.16) cm² to 0.78 (0.17) and the MSG decreased from 54 (27) to 33 (8) mm Hg (both $p < 0.001$) immediately after BAV. In only three valves was the peak AVA after BAV 1.0 cm². At five minutes the AVA decreased to 0.73 (0.16) and at 4 weeks to 0.70 (0.15) (NS). The MSG increased at five minutes to 35 (10) and at four weeks to 40 (11) (NS). Radiographs showed fractures of calcific deposits almost exclusively at the site of commissural splitting. In six valves stretching alone, without commissural splitting occurred and these had a smaller increase in AVA (32% *v* 60%) and a lesser fall in MSG (21% *v* 48%).

Significant though small haemodynamic improvements were obtained by BAV using a 20 mm balloon. These were more pronounced with commissural splitting than with simple valve stretching alone. At five minutes after BAV there was already a partial reversal of these peak effects which then persisted up to four weeks in the absence of body repair mechanisms.

Aortic root abscess complicating aortic valve endocarditis

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Development of aortic root abscess (ARA) in the course of infective endocarditis is a major determinant of the outcome of the disease. In a retrospective study of 49 patients (40 men and 9 women; median age 53, range 21–80) referred to a cardiothoracic centre with aortic valve endocarditis between 1982 and 1987, 42 patients underwent aortic valve surgery; 23 (46%) of the 49 patients had ARA (13 with prosthetic valve and 10 patients with native valve endocarditis). Intracardiac conduction disturbance (prolonged PR interval in 13, complete heart block in three, and bifascicular block in two patients) occurred in 15 (65%) of the 23 patients with ARA and in only three (11%) of 26 patients without ARA. Echocardiography correctly identified the presence of ARA in six (23%) patients. In four (17%), presence of ARA was unsuspected preoperatively. *Streptococcus viridans* was the most common infecting organism in the whole group (42%) but no particular organism was identified as predisposing to the formation of ARA. Early postoperative paraprosthetic leak of mild to moderate severity was noted in eight (40%) of 20 patients with ARA as opposed to only two (9%) of 22 patients with ARA. Surgical mortality was significantly higher (16.6%) in patients with ARA compared with 2.4% in patients with noninfected aortic roots ($p < 0.05$).

Aortic valve endocarditis complicated by aortic root abscess formation carries a high operative and postoperative mortality and is commonly associated with postoperative paraprosthetic leak. In this series conduction disturbance on the ECG was the most common indicator of the presence of an aortic root abscess.

Comparative value of precordial and transoesophageal echocardiography in the spectrum of infective endocarditis

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We report 26 consecutive patients with clinically suspected endocarditis (all bacteriologically culture

positive) in whom the findings from standard precordial cross sectional echocardiography (PE) were compared and contrasted with those from transoesophageal echo (TEE). Seventeen patients had suspected native valve endocarditis and nine had suspected prosthetic valve endocarditis (one triple valve replacement, seven aortic prostheses, and two mitral prostheses). PE suggested intracardiac vegetations in only five of 26 studies and identified no infective sequelae. TEE identified imaging evidence of vegetations in 18/26 with vegetations alone visualised in 10 patients. In eight patients vegetations plus evidence of infective sequelae were seen while in the remaining eight patients no vegetations were seen but the diagnosis was inferred by imaging infective sequelae. The infective sequelae visualised by TEE in the 16 patients included seven mycotic aneurysms, one aortic cusp perforation, five mitral chordae ruptures, four prosthetic valve dehiscences, and one left ventricular free wall intramural abscess. In no case was the infective sequelae visualised by PE. In every case TEE images were diagnostic and allowed correct clinical management decisions to be made without recourse to further investigation.

We conclude that TEE is the ultrasound diagnostic approach with the highest yield in the investigation and management of endocarditis and its complications, especially in the setting of suspected mitral prosthetic valve endocarditis and aortic root or septal infection. It would seem to be mandatory where appropriate clinical suspicions are present and precordial imaging is either equivocal or negative.

Emergency operation after failed percutaneous angioplasty: how late?

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Immediate surgical revascularisation is the ideal in reversing myocardial ischaemia after failed percutaneous transluminal angioplasty (PTCA) but this may not be always achievable. Between January 1983 and December 1987 we provided surgical cover for 667 patients of whom 25 (3.7%) came to emergency coronary bypass surgery. The revascularisation time—that is the time between the onset of the ischaemia at PTCA and the opening of the coronary bypass grafts at surgery—ranged from 160 minutes to 390 minutes, with a mean of 285 minutes. Cardioselective enzymes (creatinine kinase MB) were recorded preoperatively, and at the same time as the

ECG for three days postoperatively. Seventeen patients required a single graft, five had double grafts, two had triple grafts, and one had a quadruple graft. There were no early or late deaths, and at follow up 6-48 months postoperatively (mean 27 months), 20 of the patients were free from angina, three had mild angina, and two had moderate angina. Ten patients had myocardial infarction (MI) as shown by CKMB and ECG readings post operatively although three of these had enzymatic evidence of MI preoperatively. The mean revascularisation time of the patients who developed a MI was 250 minutes, while those who did not develop a MI had a mean revascularisation time of 280 minutes. There was no correlation between the development of a MI after surgical revascularisation and the number of grafts inserted.

Though earlier revascularisation after failed PTCA should be aimed for, it seems reasonable to carry it out up to 6½ hours after the onset of ischaemia.

Long term follow up after percutaneous transluminal coronary angioplasty in patients with chronic total occlusions

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Percutaneous transluminal coronary angioplasty (PTCA) was performed on 90 total occlusions by a single operator between December 1982 and June 1988, with a 52% (47/90) primary success rate. Acute occlusions (<2 months duration) were present in 27 (30%) with a primary success rate of 63% (17/27). Chronic total occlusion with no antegrade flow (TIMI grade 0, 1) was present in 63 (70%). The mean estimated duration of occlusion was 19 months (>2-120). All patients had severe angina pectoris with strongly positive exercise tests. Successful dilatation was achieved in 40% (25/63). The success rate was 51% in the second half of the group and 35% in the first half. The successfully dilated vessel was infarct related in 64% (16 of 25). Residual stenosis after PTCA of 15 (10%) was present with good antegrade flow (TIMI grade 3). A limited dissection was present at the site of PTCA in six (24%). Clinical and exercise assessment with cardiac catheterisation were undertaken at 18 months (>2-57) after PTCA. There was a 40 (15%) stenosis at the site of successful PTCA in 19 of 25 patients. Five patients (20%) had reoccluded; of these two had limited dissection at PTCA. One other patient had a

coronary artery vein graft. Four of five patients who reoccluded had a recurrence of angina. The remaining 19 patients with patent vessels were free of angina and had negative exercise tests.

Despite the comparatively low primary success rate of PTCA in chronically occluded vessels there is symptomatic improvement with good long term patency rates.

Importance of procedural factors in the development of recurrent restenosis after coronary balloon angioplasty

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Previously we have presented preliminary data regarding factors responsible for the development of recurrent restenosis (RRS) after coronary balloon angioplasty (PTCA). We now report the final results of our investigation conducted in all 1011 patients undergoing successful first PTCA at our centre between March 1980 and June 1987. Clinical restenosis (recurrence of angina and >50% stenosis at a site with primary success) developed in 204 patients. A second PTCA was performed in 198 of these 204 patients, with primary success being achieved in 183 (87%). Of these 183 patients, 47 (26%) developed a second restenosis of their initial lesion(s). Comparing clinical and arteriographic variables including age, degree of angina, time between PTCAs, severity of disease, and lesion morphology there were no significant differences between the 47 patients with RRS (group A) and the 136 with single restenosis (group B). Maximum balloon size and maximum inflation pressure used at the second PTCA were similar for the two groups. Univariate analysis showed that important predictors of RRS were the greater number of inflations, mean (SEM) 6.4 (0.6), in group A, 4.4 (0.2) in group B; $p < 0.0001$ and the shorter maximum inflation time (48 (4) seconds in group A, and 69 (3) s in group B; $p < 0.005$). When the longest balloon inflation time was >60 s, the incidence of RRS was 20%, as opposed to 40% when it was ≤60 s ($p < 0.05$).

These data suggest that the incidence of recurrent restenosis may be reduced by the use of fewer, more prolonged inflations when dilating initial restenosis.

Management and outcome of patients with recurrent restenosis after coronary balloon angioplasty

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Patients who develop restenosis (R) after first coronary balloon angioplasty (PTCA) are generally treated with a second PTCA. Less, however, is known about the management of patients who develop a second restenosis after repeat PTCA. To determine the outcome of such patients we reviewed the records of all 1162 patients undergoing PTCA at our centre between March 1980 and June 1987. Initial angioplasty was successful in 1011 patients (87%). Two hundred and four patients (20%) developed clinical R (recurrence of angina and >50% stenosis at a site with primary success). Of these 198 were treated with redilatation, which was successful in 183 (92%). After the second dilatation, R developed in 47 patients (26%). Of these, 41 (87%) were treated with a third PTCA, with primary success in 38 (92%). A further restenosis developed in 13 of these 38 patients (34%). Eight patients were treated with a fourth angioplasty, with restenosis occurring in four (50%). Two of these four patients underwent a fifth PTCA (with continuing success at long term follow up in both). Overall, 14 of the 47 (30%) patients who developed recurrent R were eventually treated with coronary bypass surgery. Most of these patients (33), however, were treated only with repeated angioplasties. Of these 33 patients, 27 were treated with a third angioplasty, four with a fourth procedure, and two with a fifth. Twenty nine (88%) remain free at a mean follow up of 28 months (range 8–86 months). The combined success rate for a third, fourth, and fifth angioplasty was 94%.

These data suggest that most patients with recurrent restenosis after angioplasty may be managed, both successfully and safely, with repeated redilatations.

Can exercise testing predict restenosis after coronary angioplasty?

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We investigated the ability of serial exercise testing to predict restenosis after coronary angioplasty (PTCA). Thirty one consecutive patients with single vessel disease who had successful PTCA ($\geq 30\%$ reduction in stenosis diameter measured by computerised quantitative angiography) underwent treadmill exercise testing treatment before PTCA and at three days, and one, three, and six months afterwards. All 31 patients had positive exercise tests with ST-segment depression ≥ 0.1 mV before PTCA. At angiography six months after PTCA, restenosis ($\geq 70\%$ loss of the initial gain in luminal diameter) had occurred in 14 patients (group 1) but not in 17 patients (group 2). At three days after PTCA, 11 patients in group 1 had a positive exercise test compared with three patients in group 2 ($p = 0.08$). At one, three, and six months, all 14 patients in group 1 had positive exercise tests, compared with only one in group 2 ($p < 0.01$). The ischaemic threshold was assessed by measuring the heart rate systolic blood pressure product (RPP) at 0.1 mV ST-segment depression or peak exercise if the test was negative. In group 1 the mean (SD) RPP increased from 16270 (3100) before PTCA to 20400 (3680), ($p < 0.01$), at three days, but fell to 16090 (5150) at six months. In group 2 the RPP increased progressively from 14840 (4400) before PTCA to 27372 (4177), ($p < 0.001$) at six months. A significant difference in RPP between the two groups was first seen at one month (20870 (3110) in group 1, 22177 (2913) in group 2, ($p < 0.05$)).

Patients with restenosis after PTCA show a deterioration in ischaemic threshold after the first month, whereas it progressively improves in those without restenosis. In these patients the predictive value of a positive exercise test for restenosis is 79% at three days, and 100% at one and six months, but the predictive value of a negative exercise test is 82% at three days, and 94% at one and six months.

Long term clinical follow up after coronary angioplasty for single vessel disease

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The efficacy of coronary angioplasty in selected patients with symptomatic coronary artery disease has been established, but information on the long term benefit of the procedure remains incomplete. We have analysed the acute and long term results of coronary angioplasty in 336 patients with single vessel disease (mean age 53 years, range 27–76). Before

angioplasty 74% complained of severe (grade 3–4) angina and 29% had a history of myocardial infarction. Initial angiographic success was achieved in 286 patients (85.1%), but complications occurred in 13 of these, resulting in an overall primary success rate of 81.3%. At one year 4.5% of successfully treated patients had undergone coronary surgery, and 15% had required repeat angioplasty. During follow up ranging up to five years, over 75% of all patients remained free from angina, over 80% were improved by at least two grades, and 59% were able to work. Cumulative cardiac event rates were calculated for patients with primary success. The five year cumulative freedom from coronary artery surgery was 88.0%, and from repeat angioplasty was 81.4%. The cumulative five year non-fatal myocardial infarction rate was 4.9%. Cumulative five year cardiac survival was 94.8%, both for successful cases and for all patients. Intention to treat analysis showed a five year survival from all causes of 89.3%.

These data indicate that after coronary angioplasty for single vessel disease three quarters of all patients remain free of angina in the long term, with a low risk of late cardiac death.

Hazards associated with the use of temporary pacemakers before permanent pacing

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The records of 145 consecutive patients who were treated with a temporary pacemaker before insertion of a permanent pacemaker for chronic atrio-ventricular block (110) or sinoatrial disease (35) were reviewed. The temporary pacing lead was inserted in a district general hospital in 116 (80%) and after arrival at the cardiac centre in 29 (20%). Problems were noted in 74 (51%), with at least one major problem in 52 (36%). These included failure to pace (46 episodes in 40 patients), systemic infection ($n = 9$), pericarditis ($n = 6$), haemothorax ($n = 2$), fatal pulmonary embolism ($n = 1$), and inadvertent placement in the left ventricle ($n = 1$). The incidence of problems was inversely related to local experience with the procedure. Thus temporary pacing was associated with a major problem in 7% of patients treated at the cardiac centre and 43% of patients treated in one of the 10 district general hospitals who contributed patients to this series. Furthermore, there was an inverse correlation between the incidence of problems and the number of patients referred by each district general hospital ($p < 0.05$, Spearman's rank correlation test).

These findings emphasise that temporary pacing may be ineffective and may result in serious compli-

cations, particularly when undertaken by inexperienced operators, and suggest that in many cases the risks may exceed the benefits.

New insights with computerised intraoperative epicardial mapping of QRS alternans during orthodromic tachycardia

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Electrical alternans of the QRS is reported to occur during orthodromic tachycardia. To investigate further the mechanism of QRS electrical alternans, we analysed beat to beat epicardial isochronal and isoarea maps during orthodromic tachycardia in 10 patients. Isochronal maps were generated using a 63 shock array electrode, and isoarea maps were obtained by computing the time integral of the local electrograms with reference to a baseline between the onset of R wave and the T wave offset. Isoarea difference maps were also calculated by subtracting the two successive isoarea maps. Of 13 episodes of sustained orthodromic tachycardia, 11 (85%) showed QRS alternans and the remaining two (15%) did not. Analysis of isochronal maps during orthodromic tachycardia showed that alternans in electrograms occurred in local regions and corresponded to areas with conduction delay. Beat to beat changes in total activation time were independent of alternans. There was no difference in isoarea maps or isoarea difference maps suggesting the phenomenon of alternans is associated with conduction delay rather than changes in action potential duration. Following cryoablation of the accessory pathway, atrial pacing did not induce electrical alternans. Similarly, at postoperative electrophysiological studies, atrial pacing at cycle lengths identical to those of orthodromic tachycardia did not produce electrical alternans.

These observations, not previously reported, suggest that QRS alternans in orthodromic tachycardia might be caused by local conduction delay within the ventricular myocardium.

Transoesophageal DC cardioversion

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Transchest cardioversion is a procedure of low efficiency as only a small fraction of the energy delivered passes through the heart. We have developed a stable oesophageal electrode system and describe our initial experience for elective DC countershock of atrial dysrhythmias. The oesophageal system consists of four electrodes, each of coiled gold plated copper wire mounted on PVC tubing, the external diameter of which ranges from 5–9 mm. Using this oesophageal electrode system placed 35–40 cm from the mouth to the tip of the system, we have carried out six successful cardioversions in five patients; four were in atrial fibrillation and one had recurrent atrial flutter necessitating two cardioversions within four weeks. Transchest impedances were initially recorded using R2 pads, one positioned in the right infraclavicular position, the other over the apex. Impedances were also recorded between the oesophageal system and an R2 pad on the anterior chest wall. Impedances measured with the oesophageal system (range 28–56.5, mean 42.3 Ω) compare favourably with those recorded for the same patients using chest electrodes (range 37–70, mean 55.7 Ω). Peak current at defibrillation measured in four patients ranged from 18–26, mean 22.7 A. Delivered energies for successful cardioversion ranged from 30–70 J, mean 48.5 J. Three patients had previously undergone elective countershock using the standard transchest approach, and two of these had required delivered energies of 200–360 J for successful cardioversion. All patients tolerated the procedure well and no adverse effects occurred.

Thus transoesophageal defibrillation allows successful DC conversion using much lower energies than would be required using the conventional transchest approach.

Incidence of malignant vasovagal syndrome in 332 syncopal patients: results of cardiac pacing

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Three hundred and thirty two patients with recurrent syncope underwent electrophysiological study (EPS) between January 1984 and June 1988. Complete atrioventricular block (AVB) was found in 68 (21%), intermittent block in 44 (13%), sick sinus syndrome (SSS) in 69 (21%), carotid sinus syndrome (CSS) in 32 (10%), tachyarrhythmia in 19 (6%), and no abnormality in 100 (30%). Head up tilt

testing at 60° was performed in 67 patients with normal EPS and it reproduced syncope in 50 (75%). Twelve with atrioventricular block were tilted without syncope. Two of 11 with SSS were syncopal during tilt (18%). Six of 12 with CSS were syncopal on tilt. Of 50 with normal EPS and positive tilt, 40 received DDI pacing, and 10 were unpaced. At 22 (4.3) and 20 (15.4) months follow up, respectively, 14 (35%) had continuing syncope with 1 (1.3) episodes, and in the unpaced group eight (80%) were still syncopal, with 2.75 (1.1) episodes ($p < 0.01$).

We conclude that a 60° head up tilt identifies a subgroup of patients with recurrent syncope and normal EPS who may benefit from cardiac pacing.

QT prolongation in diabetic autonomic neuropathy

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Congenital QT prolongation, which is associated with cardiac arrhythmias, may be caused by abnormal sympathetic cardiac innervation, but the effect of acquired autonomic neuropathy is uncertain. We have compared the maximum QT interval on 12 lead electrocardiograms recorded at 100 mm/second at rest in 34 diabetics and 20 normal controls. Five tests for autonomic neuropathy (heart rate response to deep breathing, Valsalva manoeuvre, and standing; blood pressure response to standing and hand grip) were scored 0 for normal, 1 for borderline, and 2 for abnormal. Diabetics were grouped as no neuropathy (score 1–3; $n = 7$), borderline (score 4–7; $n = 12$), and definite neuropathy (score 8–10; $n = 15$). The uncorrected QT interval was similar in controls (381 (28) mseconds) and diabetics (376 (31) mseconds), but the mean RR interval was significantly shorter in the diabetics (736 (106) compared with 809 (136) mseconds; $p < 0.05$). The QT plotted against RR interval was above the 95% limit for the controls in five diabetics with definite neuropathy (33%), but in none of the others. Multivariate analysis showed that RR interval alone explained 48% of the QT variability in the total sample, and RR interval and autonomic group together explained 59% ($p < 0.025$). Age, sex, or the presence of symptoms of autonomic neuropathy did not contribute significantly to QT variability.

We conclude that QT prolongation is common in diabetics with autonomic dysfunction and is a possible cause for the high incidence of sudden death in these patients.

Accuracy of a semiautomatic defibrillator during cardiac arrests

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Semiautomatic defibrillators incorporating micro-processors for the detection of ventricular fibrillation are now used in the training of paramedical and lay personnel. Using these systems clinically few have reported the results of continuous analysis of the electrocardiogram (ECG) during the cardiac arrest. The Marquette 1200 defibrillator analyses cardiac arrest rhythms in continuous 8–12 second episodes and advises whether DC shock is indicated. It was used at 57 arrests in 55 patients and in one patient who had ventricular tachycardia (VT). Initial rhythm was ventricular fibrillation (VF) in 40 arrests and was correctly identified in 37 (92.5%). Of non-VF initial rhythms 17/18 (94%) had no shock advised. Of 438 episodes VF/V flutter a shock was correctly advised in 358 (sensitivity 82%); of 80 incorrectly identified 52 had cardiopulmonary resuscitation, 19 were low amplitude (<0.25 mV), in eight VF started late in the episode, and one had jagged wide complexes resembling wide QRS complexes throughout the VF. Of 4157 non-VF episodes no shock was advised in 3901 (specificity 94%). False positive identification occurred during cardiopulmonary resuscitation ($n = 112$), VT ($n = 98$), slow sinusoidal rhythms ($n = 4$), agonal rhythms ($n = 21$), generalised fitting ($n = 6$), frequent ventricular extrasystoles ($n = 9$), and high ST segment rise causing QRS distortion ($n = 3$). During analysis, in three episodes a late change to non-VF occurred.

Excluding episodes with cardiopulmonary resuscitation, a high sensitivity of 91% (304/334) and specificity of 96% (3543/3687) for VF detection were recorded.

Stress testing: a district audit

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The safety and consequences for patient management of 777 consecutive exercise electrocardiograms (ECG) undertaken over a two year period were reviewed. The usual indications for testing were for the diagnosis and assessment of angina, but included post myocardial infarction patients. All tests were

maximal and patients were on no treatment. There were no deaths, episodes of ventricular fibrillation, or myocardial infarctions during or within 24 hours of the test. Twelve patients developed exercise induced arrhythmias, all of which were self limiting. Two hundred and eighty three (36%) patients had positive exercise ECG, and 153 (19%) had angina. Ninety one patients (13% women; 87% men) were referred for coronary angiography, either because of strongly positive exercise tests or because they had less strongly positive tests but an inadequate response to medical treatment. Twelve patients were referred for angiography without exercise ECGs, mainly for unstable angina. Sixty one per cent of patients undergoing angiography (8% women; 92% men) were referred for coronary artery surgery or angioplasty. During this period of the review 42 exercise isotope ventriculograms, 4 exercise thallium scans, and 20 dipyridamole thallium scans were also undertaken within this district.

Our annual rate per million population was 2158 exercise tests, 286 coronary angiograms, and 175 bypass operations or angioplasties; the regional average is 188 operations or angioplasties. Exercise testing within a district general hospital is a safe and cost efficient means of selecting patients for coronary angiography and surgery.

Is left ventricular dysfunction in mitral stenosis caused by isolated posterobasal wall abnormality?

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In order to determine the mechanism and prevalence of left ventricular (LV) dysfunction in mitral stenosis (MS), the left ventriculograms of 192 patients mean (SD) age 49 (11) years with mitral valve mean gradient of 10–22 mm Hg were analysed. Three cycles of non-post extrasystolic beats were analysed per patient. Left ventriculograms from 25 patients aged 47 (7) years without valvar or coronary artery disease were used as control. Regional wall motion (RWM) was derived from the fractional shortening, from diastole to systole of six hemiaxes along the long axis. Compared with normal control, mean LV ejection fraction (EF) was significantly reduced in MS (65 (14%) compared with 73 (76%), $p = 0.003$). One hundred and sixteen patients had reduced EF ($<64\%$). The mean left ventricular end diastolic volume index (LVEDVI) and left ventricular end systolic volume index (LVESVI) of the study and control of patients were 95 (49) ml/m², 112 (26)

ml/m², $p = \text{NS}$; 34 (26) ml/m, 30 (11) ml/m², $p = \text{NS}$; respectively. Abnormal EF was associated with reduced homogenous RWM. Compared with control the mean anteroapical and inferoapical wall motion were reduced in MS (49 (18)% compared with 60 (18)%, $p = 0.006$, and 52 (18)% compared with 63 (15)%, $p = 0.004$, respectively). Post-erobasal wall motion was comparable in both MS and control but less than apical wall motion in both groups.

Thus in MS there is reduced apical rather than posterobasal wall motion, but reduced systolic performance is associated with homogenous wall motion abnormality.

From peripheral to coronary arteries: experience with percutaneous laser thermal angioplasty

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The femoral artery—a testing ground for angioplasty advances applicable to coronary artery disease—is a larger calibre, straighter, motionless vessel with less spasm potential and a shorter percutaneous route to the lesion than the coronary vessels. Peripheral artery laser probe (LP) angioplasty is performed with an inflexible 2.0 mm oval metal tipped fibre enabling comparatively forceful coaxial advancement. We used the LP to cross eight of 10 peripheral occlusions (range 1–11 cm) but in none was the LP channel alone of adequate calibre before balloon dilatation. More flexible 1.3–1.7 mm tip “over the wire” LPs were developed to gain access to the coronary tree. In two patients with circumflex artery stenoses we found the loss in axial force was critical: in neither could the lesion be crossed during energy delivery, with a perforation in one (which sealed spontaneously); in the other exchange to a balloon led to a successful dilatation. Our cadaver studies showed that a vessel:probe diameter ratio of 2.0:1 was optimal to minimise lateral wall damage. In a patient with a 95% LAD stenosis a probe with vessel:probe ratio of 1.7:1 was able to cross the lesion “cold” but intractable spasm occurred after energy was delivered to debulk the lesion.

Coronary LP angioplasty is likely to find its most useful role in total occlusions by creating the initial “break through” channel while simultaneously avoiding contact with normal endothelium and lateral heat transmission to the medial coat. New LPs maintaining axial strength with optimal tip size and

combined with a balloon are to be tested next in short segment coronary occlusions both peroperatively and during percutaneous angioplasty.

Prospective study of the frequency of phrenic nerve paralysis after cardiac surgery in children

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In retrospective studies damage to the phrenic nerve during cardiac surgery has been reported in 1.3–1.6% of cases. Diaphragmatic paralysis can be an important cause of postoperative morbidity, especially in infants, because of its essential role in respiration. This prospective study was undertaken to determine the frequency of phrenic nerve paralysis after cardiac surgery in children. Sixty patients undergoing palliative or corrective surgery for congenital heart disease have been studied pre and post-operatively. Their ages ranged from one day to 14.5 years (median 17 months). The phrenic nerve was electrically stimulated percutaneously at the posterior border of the sternomastoid muscle at the upper edge of the thyroid cartilage. The diaphragmatic muscle action potential was detected by surface electrodes at the seventh intercostal space at the anterolateral aspect of the chest wall. Thirty five patients had median sternotomies, 19 left lateral thoracotomies, four right lateral thoracotomies, and two bilateral thoracotomies. Four patients (6.6%) had phrenic nerve palsies, all on the left side. Two of these had their initial operations at 2 days of age and subsequently required surgical plication of the diaphragm for episodes of respiratory distress.

Early detection of phrenic nerve injury helps plan postoperative management of the respiratory system.

Transvenous His bundle ablation: short term and long term (6–36 months) results in 15 patients. Can success be predicted?

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Fifteen patients with drug resistant supraventricular tachycardia (SVT) exhibiting a satisfactory unipolar His potential recording underwent transvenous electrical ablation of the bundle of His to achieve com-

plete heart block (CHB). Patients received either two consecutive unipolar shocks (group 1) or a single unipolar shock (group 2) from a defibrillator (350 J), or from a "National Heart Hospital" ablator (35 J) through the distal pole of a bipolar 6F USCI electrode. In group 1 (seven patients) acute CHB was achieved in all patients, with a wide QRS escape in five and a narrow QRS escape in two. One of the narrow QRS escape resumed atrioventricular (AV) conduction in right bundle branch block (RBBB) 24 hours later with the return of the tachycardia, but this was controlled by drugs. The other together with six in wide QRS escape, continued in CHB during the long term follow up. In group 2 ($n = 8$) acute CHB was achieved in five patients, with a wide QRS escape in two, and a narrow QRS escape in three. The remaining three resulted in RBBB with patent AV conduction. The two in wide QRS escape have remained in CHB during long term follow up. Those with narrow QRS escape resumed AV conduction in RBBB within 24 hours of the procedure. In all five unsuccessful patients tachycardia returned that was poorly controlled on drugs. Repeat attempt by single shock in three resulted in acute CHB with a wide QRS escape in one and a narrow QRS escape in two, both resuming AV conduction in RBBB. One with wide QRS escape remains in CHB 20 months later. In the two repeat unsuccessful cases, one required a third attempt by double shock technique to achieve CHB, and the other developed CHB spontaneously three months later.

We believe that by the conventional technique, successful electrical ablation of the His bundle generally requires high cumulative energy. Relief from tachycardia is usually not obtained by partial conduction damage. Recording of a satisfactory His bundle potential does not always guarantee success. A wide QRS escape rhythm seems to be a positive predictor of a successful ablation.

Are Doppler diastolic indices associated with functional capacity in patients with hypertrophic cardiomyopathy?

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Diastolic flow velocity waveforms obtained with pulsed wave Doppler have been used to assess left ventricular diastolic performance in patients with hypertrophic cardiomyopathy (HCM). The association between Doppler derived indices with the

patient's symptomatic state has not previously been ascertained. Complete echo Doppler studies and exercise testing with measurement of oxygen consumption (VO_2) and anaerobic threshold were performed in 72 consecutive patients with HCM and sinus rhythm. Thirty six normal individuals also had echo Doppler studies for comparison. Early (E) and late (A) mitral peak velocities (cm/second), E wave duration (DF) (mseconds), and E wave deceleration (EF) (cm/second^2) were measured. Patients with HCM differed from normals in every Doppler index: $E = 55 (16) \text{ v } 62 (13)$, ($p < 0.03$), $A = 46 (21) \text{ v } 39 (10)$, ($p < 0.04$), $DF = 300 (9) \text{ v } 231 (38)$, ($p < 0.001$), and $EF = 283 (178) \text{ v } 457 (127)$ ($p < 0.001$). Thirty one patients had an intraventricular gradient and those had higher A waves than the rest of the group ($55 (2) \text{ v } 45 (19)$, ($p < 0.05$)). There was no association between Doppler indices and the patients' functional class according to the New York Heart Association classification. The peak E and A waves were associated with VO_2 ($r = 0.415$ $p < 0.01$, $r = -0.381$ $p < 0.02$) and anaerobic threshold ($r = 0.355$ $p < 0.02$, $r = -0.35$ $p < 0.05$).

Doppler echocardiographic indices identified and defined the abnormalities in left ventricular filling in patients with HCM. Although these indices measured at rest did not correspond to the patients' professed symptomatic state, they were a strong indicator of functional capacity assessed by VO_2 and anaerobic threshold.

Evidence for increased tissue type plasminogen activator inhibitor complexes in atherosclerotic patients

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Impaired endogenous fibrinolysis in blood may contribute to the development of, or be a consequence of, atherosclerosis (AS). Because of the known circadian fluctuation of fibrinolytic components in blood, we took three hourly venous samples over 24 hours in six patients (mean age 65 years) with angiographically documented diffuse AS and in six normal subjects (N, mean age 28 years) and measured plasma concentrations of tissue type plasminogen activator (t-PA) antigen (Ag) by ELISA (ng/ml) and of t-PA activity by parabolic rate chromogenic assay (mIU/ml). Specific t-PA activity was calculated as the activity:Ag ratio (mIU/ng).

In both AS patients and normal subjects t-PA Ag showed a sinusoidal circadian variation (peak *v* nadir: $p < 0.01$) with similar phase (peak: nine hours, nadir: 21 hours) and similar amplitude (3 ng/ml). In AS patients, however, mean (SD) t-PA Ag concentration over 24 hours was raised: 14 (1) *v* 5.5 (1) ng/ml (AS *v* N, $p < 0.0001$). Specific t-PA activity also showed sinusoidal circadian variation ($p < 0.05$) in both AS patients and normals, with similar phase (peak: 18–21 hours, nadir: 3–6 hours); mean 24 hour concentration was, however, lower in AS *v* N (11 (14) *v* 72 (70) mIU/ng, $p < 0.05$) and the amplitude of change smaller (39 (35) *v* 190 (129) mIU/ng, $p < 0.05$).

In conclusion, compared with normals, patients with AS have a similar circadian pattern of t-PA Ag and specific t-PA activity in plasma; in AS patients, however, t-PA Ag concentration is increased by 150% and specific activity decreased by 85%, suggesting increased formation of circulating t-PA inhibitor complexes. The comparative role of age compared with AS merits further investigation.

Indium-111 labelled monoclonal antimyosin antibody for the detection of myocardial necrosis in subendocardial infarction and unstable angina

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The distinction between subendocardial infarction and unstable angina is a common clinical problem. We describe the use of indium-¹¹¹ labelled monoclonal antimyosin antibody (AMA) antigen binding fragment to detect and localise acute myocardial necrosis in patients with subendocardial infarction ($n = 7$) and unstable angina ($n = 7$). Subendocardial infarction was defined as chest pain with no Q waves, persistent ST and T wave changes, and a rise in creatine kinase to more than twice the upper limit of normal. The criteria for unstable angina were transient ST/T wave changes in the presence of chest pain, with normal cardiac enzymes. AMA was injected intravenously within 48 hours of the onset of chest pain. Images were acquired at 24 and 48 hours in three projections and graded in intensity (0–4) by two independent observers. All patients with subendocardial infarction had positive AMA images (grade 2, $n = 3$; grade 4, $n = 4$) that were diffuse and poorly localised. Five of the patients with unstable angina, however, also had positive images (grade 2, $n = 3$; grade 3, $n = 2$). The remaining two were

negative (grades 0 and 1). The positive images in unstable angina tended to be diffuse and corresponded poorly with the site of transient ST and T wave changes. In all but three patients (subendocardial infarction, $n = 2$; unstable angina, $n = 1$) there was no difference between the 24 and 48 hour AMA images.

This study indicates that diffuse myocardial necrosis may occur in patients with "unstable angina" as well as those with "subendocardial infarction" despite an absence of an enzyme rise in unstable angina. The image patterns are similar to those previously reported with technetium labelled pyrophosphate.

Improvement of subclinical left ventricular dysfunction in obese subjects after weight loss

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Radionuclide ventriculography was performed at rest (R) and during exercise (Ex) in 34 obese subjects weighing +30% their ideal body weight (Wt) before and after weight loss (four week supervised diet of 330 kCal in hospital). Fourteen were hypertensive (Ht) with blood pressure (BP) $> 160/95$ mm Hg, nine had coronary artery disease (CAD), and 11 were asymptomatic normotensive (Nt) subjects. After dieting the mean (SD) body weight in the whole group fell by 9.6 (3.5) kg ($p < 0.0001$), and the BP fell from 151 (21)/92 (14) mm Hg to 134 (18)/82 (11) mm Hg, $p < 0.0001$, respectively. In the subgroups, there were similar falls in both systolic and diastolic BP. Weight loss produced an overall reduction in mean resting left ventricular ejection fraction (LVEF) from 61 (10)% to 56 (7)% ($p < 0.005$). Response to Ex showed a fall in LVEF by 2 (7)% (NS), which reversed after weight loss increasing by 5 (4)% ($p < 0.0001$). The Ht group showed the most pronounced changes, where weight loss produced a fall in mean (R) LVEF from 66 (8)% to 57 (6)% ($p < 0.0005$), and a fall in Ex LVEF of 6 (9)% (NS) was reversed to become an increase of 7 (4)% ($p < 0.002$). The CAD showed similar but insignificant changes. The Nt group also showed a fall in (R) LVEF after dieting, but the Ex LVEF increased by less than 5% from its resting value which after weight loss showed a significant improvement of 6 (2)% ($p < 0.001$).

These data suggests the presence of subclinical left ventricular dysfunction in obesity which may be corrected by weight loss and a fall in BP.

Cardioscint: a new system for the continuous evaluation of left ventricular function

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A new portable bedside monitoring system (Cardioscint) has been developed for continuous monitoring of left ventricular (LV) function using a miniature CsI/photodiode scintillation detector (45×40 mm) and an Olivetti M24 computer (CsD). Special purpose modules inside the computer perform signal processing, and gated or beat to beat LV activity curves are continuously displayed together with an averaged ECG from which ST segment values are obtained. At the end of each acquisition the ejection fraction (EF), relative volumes, diastolic filling parameters, and ST value are displayed, and can be trended or stored on disc, or both. Validation was performed on 15 patients undergoing gamma camera (G) radionuclide ventriculography within 20 minutes and 6 hours later. The mean (SD) difference between CsD and G was 5.6 (7.9)% (early) and 4.5 (7.3)% (late), (range of EF: 20%–78%).

Thus the portable probe system can accurately measure LV ejection fraction, and the accuracy was maintained after 6 hours. The small size and low cost of this system make it suitable for long term monitoring and the rapid response time allows accurate LV function assessment following acute interventions.

Role of signal averaged electrocardiograms compared with myocardial biopsy specimens in ventricular tachycardia associated with no obvious cardiac abnormality

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Primary myocardial abnormalities in patients with ventricular tachycardia (VT) suggest adverse prognosis. To assess the value of signal averaged electrocardiograms (ECG) in predicting abnormal endomyocardial biopsies, 38 patients (mean age 42, range 15–70 yrs), with VT were investigated. All had normal QT interval, and coronary angiography, and no regional wall motion abnormalities. High gain signal averaged ECGs were performed using Simon's technique. Late potentials were defined as present if the duration of the filtered QRS was greater than 110 ms and the root mean square of

voltages in the last 40 ms was less than $25 \mu\text{V}$. Right and left ventricular biopsy specimens (average 5.7/patient) were reviewed on light microscopy by an independent pathologist. Fibrosis in the specimens was quantified by a point counting method and compared with a control group of myocardial biopsy specimens ($n = 24$) from subjects who had died accidentally and who had normal hearts at necropsy. In these the proportion of collagen to muscle was $<10\%$; 15 (40%) patients had abnormal biopsy specimens, six of these had late potentials that were seen in only one of the patients with normal biopsy specimens ($p < 0.001$). In all patients with late potentials and abnormal biopsy specimens the relative amount of collagen was $>15\%$ and the biopsy specimens showed moderate interstitial fibrosis. In patients with abnormal biopsy specimens and no late potentials, collagen was $<15\%$ and the biopsy specimens showed mild sub-endocardial fibrosis or fatty infiltration. Other findings in the abnormal biopsy specimens were cellular hypertrophy and atrophy. No patients had changes to suggest myocarditis. Late potentials were 96% specific and 40% sensitive for abnormal biopsy specimens with positive predictive accuracy of 87%.

Thus in patients with VT and clinically "normal hearts", the pretence of late potentials was suggestive of abnormal endomyocardial biopsy specimens with a moderate increase in fibrosis.

Normal and stenotic aortic valve area measurement: comparison of an in vitro physiological method with Doppler echocardiography

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Aortic valve (AV) area (A) estimation in patients with aortic stenosis using Doppler echocardiography (DOP-ECHO) has been found to correlate well with invasive Gorlin AVA estimations. Neither method, however, has been well validated with operative or necropsy AVA measurements which in themselves are not physiological. The Gorlin formula is also known to over or under estimate AVA at high and low cardiac outputs, respectively. In an attempt to measure accurately the physiological AVA in intact valves we mounted such AVs in a pulsatile flow rig. Saline at 37°C was delivered at flow rates from 1–5.4 l/minute with ejection periods of 25–45% and a heart rate of 70/minute. AV motion was videotaped with a magnifying lens to permit derivation of leaflet infor-

mation and the AVA was planimetered off the screen. Fifteen stenotic AVs removed at operation were compared with five normal necropsy AVs. Normal AVs showed a linear increase in AVA with flow up to our maximum 5.4 l/minute. There was no change in AVA area at any flow rate in six stenotic AVs, while nine showed a small increase (mean 20%) up to 3 l/minute flow, but none beyond this. In stenotic AVs with mobile leaflet(s) the opening rate was a fraction of that seen in normal AVs (6.3 cm/s *v* 28.2 cm/s). Preoperative DOP-ECHO derived AVA in the stenotic AVs using the continuity equation ($AVA = \text{Left Ventricular Outflow Tract (LVOT) diameter} \times \text{ratio of LVOT/AV velocity—time integrals}$) correlated well with our physiologically derived anatomical AVA ($r = 0.83$, $p < 0.001$).

Gorlin formula inaccuracies in AVA estimations are not due to changes in AVA because this is constant except at low flow rates. DOP-ECHO is an accurate non-invasive method for AVA estimation.

Demonstration of the fatigue and slow recovery in the human atrioventricular node

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Atrioventricular nodal response to an abrupt increase in the atrial rate has a complex pattern and varies according to the stimulation protocols. The "fatigue phenomenon" already described in the rabbit atrioventricular node is defined as a time dependent prolongation in atrioventricular nodal conduction time during fast pacing rate over several minutes. The characteristics of atrioventricular nodal fatigue and recovery in man were less defined. In 12 patients, a beat to beat analysis of atrioventricular nodal conduction (AH interval) was done during atrial pacing over periods of 30 seconds to two minutes. Computer assisted analysis of digitised signals (sampling rate: 2 KHz) from tape recordings was used. The basic cycle lengths were 800 or 700 ms. Fatigue was determined during fast atrial pacing cycle lengths of 500 or 400 ms and the recovery was determined during return to basic cycle length. In all cases, an instantaneous prolongation in the atrioventricular nodal conduction was observed at the onset of the fast rate which stabilised with some degree of beat to beat variation in atrioventricular node conduction (5–20 ms). Upon return to the basic drive (recovery), a beat to beat decrease in atrio-

ventricular nodal conduction was observed for several beats depending on the cycle length and duration of the fast rate.

These observations suggest that fatigue and slow recovery do occur in intact human atrioventricular node and can be manifested only with fast pacing rate for long periods. These findings provide insights on the mechanisms of cycle length alteration at the onset of supraventricular tachycardia.

Magnetic resonance imaging of cardiac sarcoidosis

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Cardiac impairment by sarcoidosis is often occult but its detection is important because it most often presents as sudden death. Diagnosis is usually based upon cardiac abnormality in the presence of known sarcoidosis, but even myocardial biopsy can be unreliable. We have studied 13 patients with cardiac sarcoidosis by magnetic resonance imaging, and shown myocardial, epicardial, and pericardial abnormalities in 10. In one patient the diagnosis was established by cardiac biopsy, and in the others the diagnosis was made from proved impairment of another organ with evidence of rhythm disturbance, conduction disturbance, or heart failure. The Kveim test was positive in nine. Spin echo (TE 26 ms, 40 ms, and 120 ms), field echo (cine imaging), and inversion recovery (TI 100 ms for fat suppression) sequences were used, although not every sequence was used in each patient. The images were scored by two observers independently for areas of high signal within the myocardium, and differences were resolved by consensus. Areas of high signal were seen in seven patients, most commonly in the proximal septum and in the posterolateral wall. Epicardial thickening with high signal was seen in two, and the fat suppression sequence was used to show that the high signal was not due to epicardial fat. Using the longer spin echo sequence, the abnormalities were more obvious. Pericardial thickening was seen in three with underlying effusion in two. The cine field echo sequence provided a distinction between pericardium and effusion, which was otherwise difficult. Abnormal left ventricular wall thickness and wall motion were seen in four. No abnormality was detected in three, all of whom had rhythm or conduction disturbance without evidence of active disease.

Magnetic resonance imaging shows myocardial, epicardial, and pericardial abnormalities in cardiac sarcoidosis. Further studies are warranted to compare its sensitivity with other techniques (such as echocardiography and thallium scintigraphy) and to investigate the specificity of abnormalities.

Non-invasive measurement of phosphorus metabolism in the human heart during exercise by phosphorus-31 magnetic resonance spectroscopy

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The ratio of phosphocreatine (PCr) to adenosine triphosphate (ATP) is an important indicator of myocardial energy status and can be determined noninvasively by phosphorus-31 magnetic resonance spectroscopy (^{31}P MRS). Because many indices of cardiac function display abnormalities only during exercise, we developed an exercise protocol for stressing the heart in the confined space of the whole body magnet while collecting ^{31}P MR spectra. We compared the physiological responses of this prone exercise to those during the Bruce treadmill test and then documented the myocardial PCr:ATP ratio at rest and during steady state exercise. Six healthy normal subjects (age 25 (3) years) lay prone with the heart positioned over a double surface coil. ^{31}P MR spectra were acquired at rest over 30 minutes. They then exercised by lifting 5 kg weights attached to both feet by cables at a rate of 50/minute/leg for 30 minutes. Spectra were collected during exercise. At rest the mean (SD) heart rate/minute was 59 (10), SBP 114 (6) mm Hg, DBP 73 (3) mm Hg, VO_2 3.6 (0.4) (ml/kg/minute). The responses during the prone exercise compared with Bruce stage I were: HR 86 (19) v 91 (13); SBP 146 (16) v 133 (17), DBP 100 (6) v 73 (6), rate pressure product 12670 (3580) v 12290 (3028), VO_2 9.2 (2) v 14.5 (2.9). Technically satisfactory spectra were obtained in five subjects. The PCr:ATP was 1.56 (0.2) at rest v 1.58 (0.14) during exercise.

There is no difference in myocardial PCr:ATP between rest and exercise in normal young men using this exercise protocol. Thus in cardiac muscle increased metabolic demand at this degree of exercise is met by increased oxygen consumption without the need to break down PCr.

Association between blood pressure, left ventricular mass and free cytosolic calcium in primary hyperparathyroidism and essential hypertension

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Primary hyperparathyroidism is associated with left ventricular hypertrophy which is said to be out of proportion to mild hypertension. It has been suggested that parathyroid hormone could act as a growth factor but more recently there has been an interest in intracellular free calcium, which is known to affect vascular tone and cell growth. We therefore measured blood pressure, left ventricular mass, and platelet cytosolic free calcium using Quin 2 in 23 patients with primary hyperparathyroidism, 20 normal controls, and 22 patients with essential hypertension. Blood pressure (mean (SEM)) in the hyperparathyroid group was higher than in controls (141 (5)/85 (2) mm Hg v 123 (2)/79 (2) mm Hg, $p < 0.001$), but lower than in hypertensive patients (175 (5)/108 (2) mm Hg, $p < 0.001$). Median left ventricular mass index was 113 g/m² in the hyperparathyroid group v 87 g/m² in controls (CI -40.9 to -7, $p = 0.006$) and 143 g/m² in hypertensive subjects (CI -38 to 12), $p = 0.31$). Median $[\text{Ca}^{2+}]_i$ in the hyperparathyroid group was slightly lower than in controls (82 nM v 88 nM, CI -3.2 to 18.6, $p = 0.15$) and significantly lower than in hypertensive subjects (101 nM, CI -27.3 to -4.8, $p = 0.005$). There was no correlation between $[\text{Ca}^{2+}]_i$ and LV mass but there was a negative correlation between $[\text{Ca}^{2+}]_i$ and diastolic blood pressure in hyperparathyroidism ($r = 0.46$, $p < 0.05$).

In primary hyperparathyroidism left ventricular mass is consistent with mildly raised blood pressure. In contrast to essential hypertension, patients with high blood pressure and hyperparathyroidism show low concentrations of cytosolic free calcium.

Electrophysiological changes in an animal model of experimental chronic cardiac failure

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Many patients with cardiac failure die suddenly, presumably from ventricular arrhythmias. We have studied the electrophysiological changes in New Zealand white rabbits with experimental chronic

cardiac failure induced by the administration of adriamycin 1mg/kg intravenously twice weekly for eight weeks, and saline injected controls. Recordings of the Stimulus-R interval (Stim-T) of the paced evoked response, an index of ventricular repolarisation time, and effective refractory period (ERP) were made in conscious animals using previously implanted bipolar permanent pacing electrodes. Progressive shortening of Stim-T and ERP occurred in the adriamycin treated animals with a reduction of 12% and 14% in repolarisation and refractoriness, respectively, by week 10. No significant changes in Stim-T or ERP were found in controls. Papillary muscles from adriamycin treated animals in vitro also showed significant shortening of intracellular action potential duration and ERP compared with controls. The changes noted in the adriamycin treated animals were not attributable to a direct, acute electrophysiological effect of adriamycin nor to differences in plasma electrolytes, noradrenaline, or renin.

Shortening of ventricular repolarisation and refractory period in heart failure may represent an intrinsic mechanism predisposing to arrhythmias and sudden death.

Role of wall stress in the pathogenesis of ventricular arrhythmia

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This experimental study in 84 isolated working hearts investigated the role played by wall stress in the pathogenesis of ventricular arrhythmia and was followed by a clinical study of 58 untreated hypertensive patients. The results showed that raised amounts of wall stress were associated with an increased prevalence of ventricular arrhythmia. Acute changes in wall stress (increase or decrease) were arrhythmogenic; acute increases, however, produced the most serious arrhythmias. Cation depletion (potassium and magnesium) increased the frequency and severity of this arrhythmia. Hypertrophy protected hearts from the development of arrhythmia but also sensitised the myocardium to cation depletion. In hypertensive patients there were some interesting correlations with the experimental findings. They had a higher prevalence of arrhythmia than the normal controls, showed the protective effect of left ventricular hypertrophy, and also had a significant adverse interaction between left ventricular hypertrophy and potassium depletion.

There are several important implications from

these findings. Firstly, raised wall stress, a common occurrence in cardiac disease, may be arrhythmogenic. Secondly, left ventricular hypertrophy exerts a protective effect against this arrhythmia. Lastly, the deleterious effect of left ventricular hypertrophy is probably due to sensitisation of the myocardium by diuretic induced, cation depletion. These results may explain some mechanisms underlying sudden death in hypertension.

Cardiac sympathetic neural activity in ischaemic heart disease

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Sympathetic neural activity has a profound effect on the susceptibility of ischaemic myocardium to serious ventricular arrhythmias yet has not been systematically studied in man. Radiotracer noradrenaline (NA) kinetics were used to evaluate the effect of myocardial ischaemia on cardiac and overall sympathetic activity in man. Atrial pacing in 15 patients with ischaemic heart disease (IHD) caused angina in 13, but neither cardiac (C) nor whole body (WB) NA spillover were increased. (C: 16 (5) ng/minute before, and 20 (7) ng/minute during pacing. WB: 306 (35) ng/minute before, and 359 (45) ng/minute during pacing ($p = \text{NS}$)). Subjects with recent unstable ischaemic symptoms ($n = 10$), had, however, greatly increased basal cardiac NA spillover (24 (7) ng/minute) compared with subjects ($n = 10$) with stable angina (6 (1) ng/minute, $p < 0.001$). Low level supine bicycle exercise in 29 patients with IHD and in six controls without serious cardiac disease resulted in an increase in cardiac and whole body NA spillover in all. Patients with IHD who did not develop myocardial ischaemia on exercise and normal controls had similar increases in cardiac NA spillover (6 (1) ng/minute to 19 (2) ng/minute and 5 (1) ng/minute to 18 (2) ng/minute, respectively). Patients developing myocardial ischaemia ($n = 20$) had similar basal cardiac NA spillover (8 (1) ng/minute) but exercise values were higher (30 (5) ng/minute, $p < 0.05$). In two patients developing severe and prolonged ischaemia cardiac, NA spillover was further increased 10 minutes after exercise, while in all other subjects it had declined towards the pre-exercise value at this time.

Thus myocardial ischaemia induced by atrial pacing does not increase cardiac sympathetic tone, but myocardial ischaemia enhances the cardiac sympathetic response to exercise and a period of unstable

ischaemic symptoms causes a sustained and specific increase in cardiac sympathetic tone. These findings may in part explain the adverse prognosis and increased likelihood of arrhythmias in patients with low level exercise induced ischaemia and unstable ischaemic syndromes.

Value of colour Doppler flow mapping and digital computer analysis in the measurement of mitral regurgitation in vitro

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Mitral regurgitation (REG) was simulated in a physiological pulsatile flow model with REG orifices of 0.2, 0.6, or 2.0 mm², varying haemodynamic conditions of REG volumes, and REG pressure drop. Colour Doppler flow mapping (CDFM) was performed in velocity (VEL) variance and power modes at constant gain and 4 kHz pulse repetition frequency. For each valve, colour jet area correlated linearly with REG pressure ($r = 0.98$, 0.2 mm²; $r = 0.97$, 0.6 mm², $r = 0.98$, 2.0 mm²) but a tenfold increase in REG volume (7.2 ml/minute at 0.2 mm² v 78.4 ml/minute at 2.0 mm²) produced only a twofold increase in colour area (1.8 cm² v 3.6 cm²). Digital computer analysis with multiple alias unwrapping also provided actual VEL assignments for the blue, red, and green components of each colour pixel in the REG jet. Total jet energy estimated by the summation of all pixel VELs ($A \times V$) and the summation of the square of each pixel VEL ($A \times V^2$) correlated better with REG pressure ($r = 0.72$, $A \times V$; $r = 0.84$, $A \times V^2$) than with REG volume ($r = 0.56$ and $r = 0.50$, respectively) for all REG valves combined. Summation of the digital computer colour intensities of the power mode correlated well with REG volume ($r = 0.80$) and not with REG pressure ($r = 0.42$).

Spatial distribution of REG jets imaged by CDFM is associated with their kinetic energy and therefore with REG pressure, and results should be interpreted with knowledge of the patient's haemodynamic function. Summation of power mode information may improve quantitation of valve REG.

Is there any indication to perform ambulatory ST segment monitoring in patients with coronary disease and a negative exercise test?

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We investigated 264 patients (222 men) aged 30–77 years with proved coronary artery disease (CAD) (67 single, 81 two, 116 three vessel disease) to establish the association between the frequency and duration of silent ischaemia and a negative exercise test (Ex test). Patients underwent treadmill exercise testing (Ex test) ($n = 255$) and 48 hours of ambulatory ST segment monitoring (total = 11 389 hours); 114 patients were receiving standard antianginal drugs, and 150 were off all treatment. Of the 255 exercise tests performed, 85 (33%) were negative for ischaemia. During the 11 389 hours of ST segment monitoring a total of 600 episodes of silent ischaemia (> 1 mm ST depression for > 1 minute) were recorded. Those with a negative Ex test had a mean of 0.41 episodes of silent ischaemia, of mean duration 6.1 minutes/24 hours (total 51 episodes, 8.5%). Those with a positive Ex test had a mean of 1.93 episodes of mean duration 42 minutes/24 hours (total 549 episodes, 91.5%) ($p < 0.001$ in both cases). The association between silent ischaemia and a positive Ex test was highly significant in those patients off and on therapy. Only one patient (1.1%) with a negative Ex test had > 4 episodes of silent ischaemia/24 hours of monitoring. This patient had documented coronary spasm.

In conclusion, silent ischaemia is rare in patients with CAD and a negative Ex test, whether on or off drugs. There is little indication to perform ambulatory ST segment monitoring in these patients, except when the history is suggestive of coronary spasm, or when patients cannot undergo a meaningful Ex test.

High density lipoprotein cholesterol, triglycerides, and ischaemic heart disease: a reappraisal

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Previous British Regional Heart Study (BRHS) findings suggested that high density lipoprotein (HDL) cholesterol was not a major risk factor for IHD events. A recent overview of four American prospective studies and the BRHS concluded that all

showed a consistent inverse relationship between HDL cholesterol and IHD events. Current analysis of BRHS data concerns 417 major IHD events (fatal and non-fatal) in 7415 middle aged men followed up for 7.5 years. The relative odds of an event occurring in the highest fifth of the total cholesterol and HDL cholesterol distributions compared with the lowest fifth were 3.6 and 2.4, respectively. Adjusted for each other, and for age, smoking, systolic blood pressure, and body mass index, the relative odds were reduced to 3.5 and 2.0, respectively. Non-fasting triglycerides were measured in 5675 men with 324 IHD events in 7.5 years follow up. The relative odds of an event for the highest fifth of the triglyceride distribution *v* the lowest fifth was 2.3, and after adjustment for smoking, systolic blood pressure, body mass index, and total cholesterol was 1.3. With HDL cholesterol included in the adjustment, the relative odds fell to 0.98.

Total cholesterol remains the most important blood lipid risk factor. HDL cholesterol is relevant but of less importance. Triglycerides do not appear to have prognostic importance once other risk factors have been taken into account.

Is the site of myocardial ischaemia reproducible?

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Angina may be produced by ischaemia occurring at variable sites within the myocardium, which may be influenced by the type of stress used to induce ischaemia. The extent of this variability has been studied in 17 male patients with documented coronary artery disease and positive exercise tolerance tests in whom drug treatment had been withdrawn. In 12 patients gated thallium imaging was performed after symptom limited maximal exercise testing on both an erect and a supine bicycle ergometer. In five patients, scans were performed following two symptom limited maximal erect exercise tests four weeks apart, and a third test performed to the same workload as the initial test. Scans were reported visually semiquantitatively by two observers from the gated image for three left ventricular segments in the anterior and 45° left anterior oblique projection (LAO), and four segments in the 75° LAO projection. Perfusion defects are thought to reflect the region of maximal ischaemia. The mean difference between observers was 2(2)%. Between scans performed erect and supine there was agreement in 66% of

segments with similar degree of variations affecting the septum inferiorly. Between the two maximal tests, in 10 of 50 segments disagreement occurred, thus in 20% of segments the diagnosis changed. Similarly the diagnosis altered in 18% (9/50 disagreements) of segments between the maximal test and that performed to the same workload. In only 50% did disagreements occur in the same segments in all three tests.

In conclusion, there may be considerable variation in the region of the myocardium that seems to be most ischaemic.

Effect of exercise training on myocardial perfusion in angina pectoris

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Forty male patients with stable angina pectoris and no previous myocardial infarction were randomised to exercise training and control groups. The training group carried out daily exercise using the Royal Canadian Airforce Schedule for Physical Fitness. Myocardial perfusion was assessed initially and at one year by thallium 201 perfusion scintigraphy after treadmill exercise. Planar thallium images were recorded in the anterior 45° LAO and 65° LAO positions and analysed by circumferential profile analysis. The profiles obtained were compared with a set of profiles from patients with normal coronary arteries. The number of abnormal degrees in each view was recorded as a percentage of total circumference and the area of abnormality was also recorded as a percentage of normal curve area. The abnormalities obtained in the three views were in addition summed to produce total scores of percentage circumference and percentage area of abnormality. The training group achieved an 11.4% increase in double product on the treadmill ($p < 0.05$). In spite of this increase in cardiac work the total percentage circumference abnormality decreased from 26 (15)% to 18 (12)%, ($p < 0.01$). The total area abnormality decreased from 4.3 (4)% to 2.6 (2.6)%, ($p < 0.05$).

Analysis of individual views showed the greatest improvements in this anterior view and the 65° LAO view with lesser degrees of improvement in the 45° LAO views. This may reflect a tendency for collaterals to develop most readily between the LAD and right coronary arteries. No significant changes were found in the control group.

Clinical experience of coronary angiography by the femoral route using a multipurpose catheter (Sones technique from the leg)

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Manipulation of a multipurpose Schoonmaker catheter permits left ventricular, right, and left coronary angiography by the femoral route. We report our experience in 1137 cases over four years with five operators. Catheterisation was completed with a Schoonmaker catheter alone in 62% (710 of 1137) of cases. A second catheter was used in 28% ($n = 313$) and a third in 10% ($n = 115$) giving a mean of 1.5 catheters per case. The Schoonmaker was successful for left ventricular angiography in 97%, right coronary angiography in 83%, and left coronary angiography in 73%. The screening time was 7.34 (5.2) minutes per case, which was twice that for studies with preshaped catheters (3.75 (1.3) minutes). A learning curve was evident for the four operators without previous experience. Comparison of their first and last 50 cases showed an increase in cases completed with a single catheter from 48% to 67%. Total catheters used for the first and last 200 cases fell from 351 to 279 compared to 600 needed if Judkins catheters had been used. The mean screening time also fell from 8.3 (4.8) to 6.1 (4.0) minutes.

The change from preshaped catheters to a single catheter system has been achieved with a saving of £17300 in this series. More substantial gains are achieved after completing the learning curve with a 54% reduction in catheters used, saving approximately £16 per case. The increase in screening time fell with experience and represents a small increase in radiation exposure.

Intracoronary injections of salbutamol show the presence of β_2 adrenoreceptor mediated activity in the human heart

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In the human heart β_2 adrenoreceptors (B2ADR) constitute 20–60% of total β adrenoreceptor number, a greater proportion than any other mammal. In

vitro, human cardiac muscle strips respond to stimulation of B2ADR by increasing contractile force. The demonstration of a functional role for these receptors in intact man is confounded by the peripheral vasodilation produced by B2ADR stimulation that produces secondary cardiac effects by reflex vagal withdrawal and sympathetic activation. We gave salbutamol, a selective β_2 agonist, to three groups of six patients. The drug was injected into the right coronary artery in order to stimulate the sinoatrial node directly while avoiding peripheral vasodilator actions. Incremental doses of salbutamol were given until they caused a sinus tachycardia. As a control the same doses were injected into the aortic root where they caused no change in heart rate. In the pilot group of six patients the mean dose required to increase heart rate by 30 beats per minute (IHR30) was 2.6 μg . To confirm that salbutamol was acting via B2ADR a further group of 12 patients were studied. They were randomised to receive either practolol 8 mg intravenously (β_1 selective blockade) or propranolol 4 mg intravenously (β_1 and β_2 blockade), 15 minutes before administration of salbutamol. These doses have equal β_1 blocking activity as defined by equal inhibition of exercise tachycardia. After practolol had been given the mean IHR30 dose was 2.1 μg whereas after propranolol the mean IHR30 dose was 64 μg (practolol v propranolol $p < 0.001$).

This study shows that direct cardiac β_2 adreno-receptor stimulation in intact man has a positive chronotropic effect.

Intimal proliferation in an organ culture of human saphenous vein

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Intimal proliferation is a principal cause of late vein graft occlusion. Its aetiology is uncertain, however, partly because its progression is difficult to study in humans. To overcome this we attempted to produce intimal proliferation in an organ culture of human saphenous vein. Vein (1 cm length) was pinned out intimal surface uppermost and maintained at 37°C in 6 ml of RPMI 1640 medium containing 30% donor calf serum, 0.8 mM glutamine, 2.5 $\mu\text{g}/\text{ml}$ of gentamicin, 100 iu/ml of penicillin, and 100 $\mu\text{g}/\text{ml}$ of streptomycin. Medial viability was assessed by ATP concentration (nmol/g wet weight), endothelial integrity by scanning electron microscopy, and cell

proliferation by preincubation for 24 h with $6 \mu\text{Ci}$ of [$6\text{-}^3\text{H}$]thymidine followed by fixation, paraffin embedding, transverse sectioning, and autoradiography. Freshly isolated vein had a mean (SEM) ATP concentration of 300 (30) ($n = 16$), had about 80% of endothelial coverage, and had few dividing cells in any cell layer. Vein surgically prepared for coronary bypass grafting had an ATP concentration of 130 (20) ($n = 17$, $p < 0.001$), $< 20\%$ of endothelial coverage, and few dividing cells in any cell layer. Freshly isolated vein cultured for two weeks had an unchanged ATP concentration of 250 (30) ($n = 8$), it was covered by enlarged endothelial cells, and had many proliferating cells that were confined to the endothelial and immediately subendothelial layers. Surgically prepared vein cultured for two weeks also had an unchanged ATP concentration of 180 (30) ($n = 9$), which was still significantly lower than freshly-isolated vein ($p < 0.01$), it was $< 20\%$ covered by endothelial cells, and had a similar number and pattern of proliferating cells as cultured freshly isolated vein.

We have succeeded in showing intimal proliferation in human saphenous vein in organ culture. This was not influenced by surgical preparative damage despite the observation that neither the media nor the endothelium recovered during culture. This system provides, for the first time, an experimental model in which the progression of intimal proliferation can be studied in human tissue.

Do tight coronary stenoses impede access of cold cardioplegia: protection or not?

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The two major elements in the use of a cardioplegic technique are the high potassium concentration that is used to arrest the heart, and cooling that protects the myocardium during the period of arrest. The cardioplegic solution infused into the coronary arteries through the aortic boot may not reach myocardium beyond tight stenoses. The question arises as to whether these areas are protected by hyperkalaemic arrest. We have recorded a monophasic action potential (MAP) from the epicardium in an area supplied by either the left anterior descending or circumflex coronary arteries during infusion of cold cardioplegic solution during routine coronary artery surgery as an index of the arrival of cardioplegic solution to the area of interest. The net effect of cardioplegia on action potential duration is vari-

able due to the opposite influences of potassium (shortening) and cooling (lengthening) on repolarisation time. The effect on diastolic potential is a rapid and substantial reduction, however, due primarily to the influence of raised potassium concentration; cooling had no effect. Although measurements of diastolic potential in long term recordings may be problematical, short term recordings over a few beats are acceptable with our electrode design. Fourteen patients were studied during infusion of the cardioplegic solution using either one or two MAP electrodes. Satisfactory recordings (16) were obtained from the left anterior descending territory in 10 and circumflex area in six (both together in three). Recording from an area distal to a tight stenosis with angiographic evidence of antegrade diastolic potential fell by a mean (SD) of $3.9 (2.5) \text{ mV}$, $n = 10$. Recording from an area distal to a tight stenosis but without evidence of antegrade filling the diastolic potential fell by a mean of $0.2 (0.4) \text{ mV}$, $n = 5$. In one patient where the recording area was supplied by a non-stenosed circumflex coronary artery infusion of the cardioplegic solution reduced the diastolic potential by 4.5 mV . In three patients in whom simultaneous records were obtained from areas supplied by non-occluded and totally occluded arteries the contrasting changes in diastolic potential were striking. When a change in MAP duration (rate corrected) occurred this was always associated with a pronounced fall in diastolic potential.

Our results show that myocardium distal to tight stenoses may be electrophysiologically uninfluenced by the high potassium cold cardioplegic solution, thereby raising the question as to whether parts of the heart are inadequately protected during the procedure.

Improved patency rates to small vessels with the internal mammary graft

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Ninety five of 330 patients undergoing isolated coronary artery surgery between January 1985 and June 1987 agreed to recatheterisation and exercise electrocardiogram (ECG) one year postoperatively. These 95 patients had received 103 pedicled internal mammary artery (IMA) grafts and 272 saphenous vein grafts (SVG). Of the 330 patients, there were four hospital deaths (1%) and no late deaths. No significant difference was found between the study group (95) and the total group (330) for age ($54 \text{ v } 57$

years), sex (85% *v* 82% men), severity of disease (14% *v* 8% left main stem; 86% *v* 82% 3VD; 12% *v* 15% 2VD; or 2% *v* 1% 1VD) or number of grafts performed (6% *v* 6%: two grafts; 38% *v* 35%: three grafts; 41% *v* 46%: four grafts; 15% *v* 12%: five grafts). At one year, overall NYHA status was improved with 86% of patients in NYHA Class 0 (preoperatively 82% were in NYHA III or IV), and 92% of patients had negative exercise ECGs: 25% at stage 5, 35% at stage 4, and 32% at stage 3. Overall graft patency was 90% for IMA and 79% for SVG ($p = 0.025$, χ^2 test). The size of vessel grafted had a significant effect on graft patency when SVG was used: 82% for 2.0 mm vessel *v* 70% for 1.25 mm ($p = 0.05$), but no such difference for IMA (100% for 2.0 mm *v* 100% for 1.25 mm). Overall graft patency in women was pronouncedly worse than the total group at 54% (57% for IMA and 41% for SVG: $p = 0.01$) and this was independent of the size of the vessel grafted.

The internal mammary artery provides improved one year patency rates, which unlike saphenous vein are not related to the size of the vessel being grafted.

Late left ventricular function after anatomical correction of anomalous left coronary artery

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Seven children aged 10 weeks–10 years who underwent anatomical correction of anomalous origin of the left coronary artery (LCA) from the pulmonary artery, between 1979 and 1985, have been followed up for a minimum of 3.5 years. Five infants aged 10 weeks–6.5 (mean 4) months presented in severe cardiac failure; two of these patients (aged 4 and 6.5 months) had ECG evidence of extensive anterior myocardial infarction, and one died at operation. Two children aged 5 and 10 years presented with dyspnoea on exertion. At operation the LCA was reimplanted directly into the left coronary sinus of the aorta in all. Mitral annuloplasty was performed in one. With a follow up of 3.5–10 (mean 6.6) years, there have been no late deaths. No child is on drugs and exercise tolerance is normal. Ischaemic changes on the ECG have improved in all except one patient who had preoperative myocardial infarction. Left ventricular function has been monitored by M mode and cross sectional echocardiography, radionuclide and left ventricular angiography in all patients. Abnormalities of anterior wall motion have improved and the left coronary artery is patent on

coronary angiography with normal perfusion patterns in all patients.

It is concluded that anatomical correction of anomalous left coronary artery can be carried out safely at a young age and offers the best hope for near normal left ventricular function.

Intraoperative cerebral monitoring with a cerebral function analysing monitor predicts neuropsychological outcome after coronary artery surgery

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We have recorded cerebral electrical activity using a cerebral function analysing monitor (CFAM) in 58 patients undergoing elective coronary artery bypass surgery. All patients underwent detailed neuropsychological testing with a series of 10 tests before surgery, and at eight days and eight weeks after operation. Focal neurological deficit, unresolved at the time of hospital discharge, occurred in three patients (70% confidence interval (CI) 2.5% to 10.5%), which resolved in all but one patient by eight weeks (70% CI 0.3% to 6.2%). A deterioration in neuropsychological performance compared with preoperative scores was seen in 57% (70% CI 47% to 63%) at eight days, and 33% (70% CI 26% to 40%) at eight weeks. Abnormalities in CFAM traces were seen in 13 patients (70% CI 17% to 30%). Abnormalities were defined as abrupt changes in the mean CFAM voltage or enlargement in the voltage envelope of greater than 10% accompanied by an increase in low frequency electroencephalographic waveform activity not recovering within a three minute period. Those patients with neuropsychological impairment at eight weeks had an increased incidence of CFAM abnormality ($\chi^2 = 4.265$, $p = 0.04$), whereas there was no significant association at eight days ($\chi^2 = 0.002$, $p = 0.96$). The magnitude of neuropsychological impairment at both eight days and eight weeks was significantly greater in those patients with abnormal CFAM records ($t = 2.29$, $p = 0.02$ at 8 days; $t = 2.09$, $p = 0.013$ at eight weeks: unpaired t test). There was no association between CFAM abnormality and focal deficit at the time of hospital discharge ($\chi^2 = 0.445$, $p = 0.50$).

Abnormalities of CFAM activity are a significant predictor of diffuse neuropsychological impairment following coronary artery bypass surgery but do not predict focal neurological deficit.

Effect of aprotinin on blood conservation during cardiac surgery

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Because bleeding after cardiopulmonary bypass (CPB) remains a source of morbidity usually requiring blood transfusion, treatment with epoprostenol and desmopressin to reduce this need has been investigated. The serine proteinase inhibitor aprotinin was studied in a randomised, placebo controlled, double blind study in 80 patients having primary aortocoronary bypass grafting. Volume replacement in the postbypass period was with non-haemic colloids. Bank blood was only given if the haematocrit was below 30%. Blood concentrations of 4 µmol/l of aprotinin were obtained at the beginning of bypass. Mean (SD) chest drainage in the 40 patients given aprotinin was significantly less than the control group: 309 (133) ml v 573 (166) ml, $p < 0.01$. Total haemoglobin loss into the chest drains was also significantly reduced from 37.7 (18.3) g to 12.0 (12.6) g. Bank blood requirements were less in the aprotinin patients who received a total of 13 units. The control group received a total of 78 units. Thirty two of the treated patients were not transfused at any stage whereas 35 of 37 controls required blood. Venous haemoglobin concentrations preoperatively, and on the first and the seventh postoperative days did not differ. Template bleeding times were similar preoperatively, 90 minutes postoperatively, the increase seen in the control group was not seen in the aprotinin patients. This drug has also been used in two other groups of patients at much higher risk of bleeding—those having reoperations and those with acute sepsis at the time of surgery. In a randomised trial, 11 of 22 patients having reoperations were given aprotinin. Blood loss postoperatively was reduced from 1509 (388) ml to 286 (48) ml in the treated patients ($p < 0.001$). Only four treated patients were transfused with a total of five units of bank blood compared with all the untreated patients who were given 41 units. Fifteen patients, all requiring operation for acute infective endocarditis received a slightly higher dose of aprotinin. Five had evidence of intravascular coagulation and two were receiving dialysis. Mean blood loss in this group was 388 ml. Six patients were transfused with a total of 11 units of bank blood. No adverse effects attributable to the drug were seen.

These data show that aprotinin reduces the need for bank blood after cardiac surgery with safety. Patients who are likely to benefit most are those at high risk of postoperative bleeding, those having reoperations, those with infective endocarditis, and

those who for religious or other reasons cannot or will not have blood transfusions. Its use in cardiac surgery offers a major contribution to blood conservation.

Contraction excitation feedback: a new approach

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The Valsalva manoeuvre provides a convenient means of manipulating left ventricular volume. These volume changes result in pressure changes associated with the three phases of the Valsalva manoeuvre: (1) an initial increase in left ventricular volume and pressure as blood is squeezed into the heart; (2) a subsequent decrease caused by impairment of venous return, and (3) an increase in pressure and volume when venous return is restored at the end of the manoeuvre. It is well known that the electrical signal before any contraction influences that contraction. The reverse phenomenon whereby ventricular loading conditions influence electrical activation and hence the subsequent beat has recently been shown in man (contraction excitation feedback). Acute elevation of ventricular pressure has been shown to shorten repolarisation and hence refractoriness. We have conducted a study intended primarily to examine the interrelation of acute volume changes. Monophasic action potentials (MAPs) were recorded from the left ventricular endocardium together with femoral artery pressure during the performance of a controlled Valsalva manoeuvre (maintenance of a steady 40 mm Hg for 15 seconds). Monophasic action potential duration was measured at 90% repolarisation in two ways: comparing beats with similar preceding cycle lengths, and using a rate correction. Nine patients were studied; two had poor left ventricular function (ejection fraction of less than 20%); of the other seven patients who were receiving calcium antagonists. The effects of the Valsalva manoeuvre on MAP duration was highly reproducible. In the five patients not receiving calcium blockers and with good left ventricular function during the first few beats (phase 1) mean (SD) systolic pressure increased from 127 (12) to 184 (22) mm Hg and MAP duration increased from 353 (34) to 365 (33) ms; during phase 2 left ventricular pressure fell to 74 (18) mm Hg and MAP duration decreased to 336 (31) ms; during phase 3 systolic pressure increased to 189 (20) mm Hg and MAP duration increased to 440 (43) ms. In the two patients with poor left ventricular function a similar

pattern was observed when only minimal changes in pressure occurred, suggesting that the MAP changes were primarily as a result of volume change. In the two patients receiving calcium antagonists the MAP changes were attenuated.

Our studies suggest that acute changes in volume influence MAP duration. The changes are opposite in direction to those usually associated with pressure change. The inter-relation between pressure and volume represents a new approach to contraction excitation feedback and a breakdown in this compensatory mechanism may well be important in arrhythmogenesis.

Development of peptide containing neural and endocrine elements in the human heart

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Several peptides have been identified in mammalian cardiac nerves and myocardial cells and are thought to act as neuromodulators or transmitters, or circulating hormones, respectively. There is a lack of information regarding the expression of these peptides during human development.

We have used indirect immunofluorescence staining techniques and antisera to general neural markers, neuropeptides, and atrial natriuretic peptide (ANP) to examine neural and endocrine elements in fetal hearts ($n = 25$, 7–24 weeks' gestation) obtained after spontaneous or legal abortion. Ganglion cells and nerves were present in the atrial subepicardium from seven weeks' gestation, concentrated around the sinus node and atrioventricular junction. Ventricular innervation became apparent at about 12–14 weeks forming a prominent epicardial perivascular plexus. The density of innervation increased up to 20–24 weeks, but was always greater in the sinus and atrioventricular nodes than in other regions. Many nerve fibres contained neuropeptide Y and are probably of sympathetic origin. Other nerves displayed somatostatin or vasoactive intestinal polypeptide immunoreactivity. ANP was found from 7 weeks onwards, localised in both atrial and ventricular myocardial cells. Cells of the ventricular conduction system also contained ANP whereas the sinus and atrioventricular nodes were unreactive.

The findings show that putative endocrine elements express ANP at an early stage in the fetal heart

and there is a progressive, regional development of human cardiac innervation by nerves which may also contain peptides.

Human left ventricular twist: measurement by magnetic resonance tagging

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It has been postulated that rotation of the left ventricular (LV) apex with respect to the base (twist) is a component of normal systolic function in man but, until now, it has not been possible to measure twist non-invasively. Tagging is a magnetic resonance imaging technique which labels specific areas of myocardium by narrow selective radio frequency excitation. If applied at end diastole, the tags will move with the myocardium through systole. We have used tagging to measure non-invasively LV twist in man. Eight normal volunteers (aged 24–38) were studied in a 0.38T resistive magnet. Five short axis LV planes were obtained separately at end systole, four radial tags having been inserted at end diastole, intersecting the myocardium at eight locations. Twist was defined as the angular displacement of each epicardial and endocardial tag point from its diastolic position with the base as zero and measured using an online coordinate system and a systolic centroid. Twist of the apex relative to the base was clockwise ($20 (5.7)^\circ$, $p < 0.001$) for endocardial points and the same in all radial positions. Epicardial twist (clockwise, $11 (3)^\circ$, $p < 0.001$) was $9 (4)^\circ$ less than endocardial ($p < 0.01$), but greater ($6 (6)^\circ$) in the anterolateral than posterior positions ($p < 0.01$). Endocardial twist was not site specific.

Thus twist is a component of LV ejection in man, endocardial twist is homogeneous whereas epicardial twist is site dependent, and greater endocardial than epicardial twist suggests shearing or sliding of myocardial layers upon one another.

Myocardial hypertrophy and mechanical restitution in isolated human myocardium

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Small strips of human myocardium were obtained at open heart surgery from 58 patients; 24 patients had

aortic stenosis requiring aortic valve replacement (AS) and 34 had no evidence of left ventricular outflow obstruction (non AS). Muscle strips were mounted isometrically in a tissue bath, superfused with Tyrode's solution, gassed with 95% oxygen and 5% carbon dioxide at 37° C, and field stimulated at 1 Hz. Extra stimuli were given at varying intervals (ectopic interval) from the preceding beat (300 ms to 45 s). Mechanical restitution curves (MRC) were constructed by plotting the ratio of the peak tension of the ectopic beat and its preceding steady state beat, against the ectopic interval. The MRC described a rapid recovery phase followed by a slow decay. The rapid recovery consisted of a biexponential function (time constants τ_1 and τ_2) and the decay by a single exponential (time constant τ_3). Mean (SEM) time to peak tension was prolonged in myocardium from patients with aortic stenosis (317.3 (10.5) ms) compared to those without (287.6 (6.4) ms), ($p < 0.025$). There was no difference between peak tension or maximum rate of rise of tension (dT/dt) in the two groups. τ_1 was prolonged in the AS group (585.9 (57.6) ms), compared with the non-AS group (377.0 (28.4) ms), ($p < 0.001$). τ_2 and τ_3 did not differ significantly between the two groups. τ_1 correlated positively with the degree of left ventricular hypertrophy as assessed by echocardiographic wall thickness measurements ($p < 0.025$) and correlated negatively with the aortic valve area ($p < 0.025$).

Thus mechanical restitution in human myocardium is described by three exponential phases. Hypertrophied human myocardium is associated with normal peak isometric tension, prolonged twitch duration, and slowing of the fast recovery phase of mechanical restitution.

Evidence for active filling of the left ventricle: a study of the association of ventricular torsion and ventricular volume

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Three dimensional motion of coronary artery bifurcation points was studied. The three dimensional data were derived from computer analysis of calibrated biplane coronary arteriograms of the left coronary artery in five apparently normal patients. The arteriograms were performed at 50 frames per second and gated to the electrocardiogram. Corrections were made for pincushion distortion and magnification effects. The resulting data were cor-

rected for the translation component of cardiac motion and the final 25 to 30 three dimensional coordinates for each frame were analysed for the torsional component. A time dependent long axis formed by the maximum Eigenvector of the points for each frame passes through the time dependent centre of gravity. Rotation about this axis was studied. The points were found to rotate about the long axis, the degree of rotation of a given point directly correlating with its distance from the centre of gravity. Rotation was maximal at the base and apex in opposite directions and the greatest angular velocities occurred in early systole, early diastole, and during atrial systole. The early diastolic rotation occurred with no change in the distance from the centre of gravity—that is, during isovolumic relaxation. This was confirmed by relating the timing of the torsion to changes in ventricular volume, measured both by ventriculography in the same patients and by creating three dimensional models of the ventricles based on the coronary artery bifurcation data previously described. This showed that volume changes in early diastole follow torsional change by 60 (20) milliseconds.

This lends weight to the theory that untwisting of the coiled ventricle during isovolumic relaxation is the active initiation of ventricular filling.

An immunological marker for alcohol related myocardial disease

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The contribution of chronic alcohol consumption to left ventricular dysfunction in patients with idiopathic dilated cardiomyopathy (IDCM) and coronary artery disease (CAD) has been difficult to assess. One difficulty is the lack of a pathological marker for alcohol related myocardial disease. Recent immunological studies suggest that in alcohol related liver disease IgA may be such a marker. We examined right ventricular endomyocardial biopsy specimens from 50 patients, aged 27–65 years. The indication for biopsy was IDCM ($n = 20$), ventricular dysfunction disproportionate to the extent of CAD ($n = 24$), and ventricular arrhythmias ($n = 6$). In addition to the routine histology, sections were stained using an indirect immunoperoxidase technique for the presence of immunoglobulins (IgG, IgM, and IgA). These were then examined by an observer with no knowledge of the patients' clinical

details. Fourteen patients were heavy drinkers (> 30 u/week), eight were moderate (15–30 u/week), nine were light (1–15 u/week) and 19 drank occasionally (< 1 u/week). Twelve patients had evidence of IgA deposition on myocardial cell membranes. The diagnoses in these patients were IDCM in five and coronary heart disease in seven. Of these, nine admitted to heavy, and three to moderate, alcohol consumption.

IgA deposition on myocardial cell membranes is a highly specific and moderately sensitive marker of alcohol related myocardial dysfunction and may also have a role in the pathogenesis of this condition.

Range of coronary artery lesions and the requirement for coronary arteriography in post-infarct ventricular septal defects

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In our experience a combination of ultrasound imaging methods (cross sectional echo, continuous wave Doppler, and colour flow imaging) have effectively supplanted left ventricular angiography in the diagnosis and haemodynamic assessment of post infarction ventricular septal defects (PIVSD). The requirement for preoperative coronary angiography in such lesions remains a subject of much debate. It therefore seemed appropriate to review the coronary lesions present in large series of PIVSDs to attempt to define any correlation between PIVSD type and coronary morphology. CFM defines three distinct PIVSD types: (1) apical, (2) central trabecular, and (3) posterior. In order to determine the incidence of critical coronary stenoses in patients with PIVSD, we reviewed 112 consecutive coronary arteriograms collected from three cardiac centres. PIVSD morphology was assessed at surgery or necropsy (apical 26, central trabecular 29, and posterior 57). A critical coronary stenosis was defined as greater than 50% luminal narrowing in a first order or major second order vessel. Single vessel disease (infarct vessel only) occurred in 23/26 apical PIVSDs (88%), in contrast to 22/29 central trabecular (74%), and 26/57 posterior (46%) PIVSDs. In addition the spectrum of associated multivessel disease differed significantly between central trabecular and posterior PIVSDs with much more severe disease in the latter group.

We conclude that the requirement for pre-

operative coronary arteriography seems to differ significantly between the three PIVSD types. In our experience coronary arteriography may be superfluous in the apical and central PIVSD groups but may be mandatory in the posterior PIVSD group.

Using the Rose angina questionnaire

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Since Rose introduced his questionnaire on chest pain brought on by exertion as an epidemiological method of determining angina in 1962, it has been extensively used in many countries. The self administered version introduced in 1977 has proved particularly useful in postal surveys. We report on two methodological issues based on our experience in the British Regional Heart Study (BRHS): (1) Most reports have restricted themselves to reporting on "definite" angina (that is, chest pain brought on by exertion, situated in the sternum or left anterior chest, which forces a person to slow down or stop and which disappears within 10 minutes). We argue that there is a loss of sensitivity and no useful gain in specificity by imposing the criteria additional to exertion. In the BRHS, men with "possible" angina (that is, chest pain on exertion, but not satisfying all the other criteria) had similar rates of ECG abnormalities to those with "definite" angina. Of men with definite angina, 45% could recall a doctor telling them they had ischaemic heart disease, compared with 30% of men with "possible" angina, and 2.5% of other men. Most importantly, individuals with "possible" angina were at the same risk of heart attack during 7.5 years follow up as men with "definite" angina. (2) In the BRHS the age standardised prevalence of angina was the same whether assessed by administered questionnaire, as at the initial screening, or by a postal questionnaire filled in by 99% of survivors five years later. This is at variance with reports that claim a doubling of prevalence estimates when a self administered questionnaire is used.

Prevalence of heart failure in two general practices

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There is little information on the epidemiology of heart failure. The Framingham study, 20 years ago, suggested a prevalence of 1%. The current study assessed the prevalence in two large (20 000 patients) general practices in north west London. It was assumed that patients who had heart failure would be on diuretics and in a three month period would have to receive prescriptions from the general practitioner. Consequently, all patients in the practices receiving diuretic prescriptions over a three month period were noted, and a subsequent analysis was made of their practice records, which included hospital correspondence. In each of the two practices, the number of patients with heart failure was the same. The total number was 66 patients, a prevalence of 0.3%. There were 32 women and 25 men with a mean age of 72.5 (10.3) years. Only 11 patients were under 65 years old. The aetiology was thought to be coronary artery disease in 36, valve disease in 13, hypertension in four, and unknown in 13. The initial diagnosis of heart failure was made in hospitals in 51, and solely by the general practitioner in 15. Irrespective of whether the diagnosis had been made in hospital or by the general practitioner, only 60 patients had an ECG, only 58 a chest radiograph, and only 13 echocardiography. In one practice, of 90 patients taking diuretics, 41 were for hypertension (46%), 34 were for heart failure (38%), and the remainder were for leg oedema, "needing to pass more urine", and so on.

In the population studied, heart failure was less common than is generally believed and is predominantly a problem in the elderly. A cardiac abnormality is only proved in a minority of patients. Contrary to popular teaching, hypertension is an uncommon cause of heart failure.

Effects of digoxin in infants with ventricular septal defects and cardiac failure

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The clinical and haemodynamic effects of digoxin in infants with ventricular septal defect (VSD) and cardiac failure have been studied prospectively in 13 infants (mean age = 3.5 months, range 1–6 months). After stabilisation of other antifailure treatment, infants were given digoxin or placebo in a randomised double blind cross over trial. Clinical, echocardiographic, and Doppler measurements together with serum digoxin concentrations were assessed at baseline, 4–8 hours after a loading dose, and after one

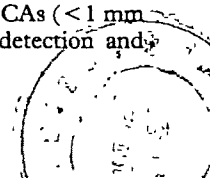
week of long term treatment. In all 13 infants data were obtained on the acute effects of digoxin and in 10 on maintenance treatment. Serum concentrations of digoxin were in the therapeutic range in both the short (mean = 1.3, range = 0.6–2.3 µg/l) and long term (mean = 1.2, range = 0.6–2.3 µg/l) phases. During the short term there was an increase in fractional shortening (FS) ($p < 0.01$) but this was not associated with a change in heart rate (HR), respiratory rate (RR), left ventricular ejection time (LVET), stroke volume (SV), or pulmonary to systemic blood flow ratio (Qp/Qs). During long term treatment the HR fell ($p < 0.001$) but so did LVET ($p = 0.05$), and there was no change in RR, FS, SV or Qp/Qs. These results show that after the short term administration of digoxin there was an isolated increase in FS. During long term treatment the fall in heart rate was not associated with improvement in other measurements and might simply reflect the action of digoxin on the sinus node.

The study suggests that digoxin is of no benefit in treating cardiac failure in infants with VSD.

Densitometric angiographic assessment of normal and diseased coronary arteries: validation of technique

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Computer assisted quantitative analysis (QA) systems for coronary arteriograms are now commercially available, but their ability to measure dimensions of diseased coronary arteries (CA's) accurately has not been fully evaluated. A QA facility with some original features has been developed. To validate the algorithms used, segments of normal and diseased CAs were excised at necropsy, perfuse fixed, filled with 5% barium sulphate gel, decalcified, and set in wax blocks. x ray films were taken from two approximately orthogonal views using both screen film and cine fluorography, both without scatter material and with a plastic bone phantom to provide realistic scatter flux. The films were digitised, mask subtracted, and analysed with the QA facility. Photographs of the exposed sections of the blocks were taken as they were serially cut with a 5 µm microtome. The true cross sectional area of the CAs were measured. This technique ensured accurate registration of measurements and ensured that the CAs did not change dimensions between the x ray picture and cutting. For normal CAs (<1 mm to >4 mm in diameter) both edge detection and



densitometric analyses were more accurate than those calculated from edge detection data only. Densitometric units were converted to true dimensions. For diseased CAs with screen film, linear regression yielded a slope of 1.13, correlation coefficient 0.97 for 84 samples, standard error of the estimate (SEE) 0.47 mm². Correlation of 29 measurements of estimated area from the cinefilms with scatter material gave a correlation coefficient of 0.97, slope 1.05, SEE 0.47 mm².

We conclude that this system provides valid estimates of lumen dimensions in normal and diseased segments of CAs.

Haemodynamic assessment of mitral stenosis in the presence of atrial fibrillation

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In patients with atrial fibrillation (AF) the haemodynamic assessment of mitral stenosis (MS) is complex, requiring measurement of the mean valve gradient over 10 cycles, and the cardiac output. We describe a new method for assessing the severity of MS which is reliable and simpler to perform. In 20 patients with MS and AF, PAW and LV pressures were recorded simultaneously. The end diastolic pressure gradient was related linearly to RR interval in each patient and was unchanged by exercise. The slope (S) and intercept (I) varied with the degree of MS, and correlated with the Gorlin valve area (G): $S = 10.4(G) - 1.7$, $r = 0.8$, $p < 0.005$; $I = 1460 - 662(G)$, $r = 0.9$, $p < 0.005$. The area (A) between PAW and LV diastolic pressure signals was measured and rose with increasing RR interval to a plateau (A-max). A-max correlated closely with the Gorlin valve area: $A\text{-max} = 21.1 - 9.9(G)$, $r = 0.9$, $p < 0.001$. Thus in MS complicated by AF, the relation between RR interval and end diastolic gradient permits accurate assessment of severity of stenosis by calculation of simple parameters (S, I, A-max) for which we have derived regression equations; they enable the construction of nomograms relating end diastolic pressure gradient to Gorlin valve area at different heart rates.

The method correlates closely with the Gorlin valve area but is simpler to perform, being independent of cardiac output measurement and heart rate.

Demonstration of myocardium at further risk after thrombolysis in acute myocardial infarction

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Although thrombolysis reduces mortality in myocardial infarction (MI), the extent to which it may salvage myocardium in individual patients has not been shown. Accordingly, 15 patients treated with streptokinase in acute MI were studied during early elective percutaneous coronary angioplasty (PTCA) to a patent infarct related artery. Left ventricular (LV) performance before and during PTCA was examined with intravenous DSA and analysed using both regional wall motion and phase/amplitude methods. During balloon inflation maximum ST elevation (mean 3.1 mm) was seen in 13 patients while mean LV ejection fraction (EF) fell in all cases (from 60% to 47%, $p < 0.001$) despite pre-existing Q waves in nine patients. In the eight patients undergoing LAD PTCA the fall in LVEF (54% to 40%, $p < 0.001$) was associated with a reduction in apical regional shortening (19% to 1%, $p < 0.01$). LVEF fell similarly in seven patients during right coronary PTCA (68% to 55%, $p < 0.001$) associated with a reduction in inferior shortening 41% to 16%, $p < 0.01$). Phase amplitude analysis showed similar regional abnormalities in 13 patients.

A deterioration in LV performance during balloon coronary occlusion in these patients suggests that thrombolysis had salvaged myocardium at risk during thrombotic occlusion. In patients with pre-existing Q waves, LV ischaemia during balloon inflation implies that this ECG abnormality does not necessarily indicate completed infarction.

Use of Doppler echocardiography in determination of left ventricular dP/dt max

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Doppler echocardiography is emerging as a powerful tool in measuring indices of left ventricular contractility. In human subjects peak acceleration has been shown to correlate closely with ejection fractions, and in dogs peak aortic flow velocity has been shown to correlate closely with maximum dP/dt. Our study verifies the correlation of peak velocity with

dP/dt max in human subjects and validates our theoretically derived formula that showed a better correlation with dP/dt max. Using the concept for conservation of energy, by assuming sinusoidal aortic flow and pressure patterns and a constant of proportionality between the area of LV outflow and ascending aorta, the following is derived:

$$dP/dt \max = \frac{Vp^2}{T} + \frac{\text{pulse pressure}}{TC} (\text{pulse } P); \text{ where}$$

K = constant; T = time to peak velocity; Vp = peak velocity; and TC = corrected ejection time. The validity of this equation was tested in 11 patients undergoing diagnostic catheterisation using a catheter tip micromanometer in the LV for dP/dt max and a 4 MHz continuous wave Doppler transducer for aortic flow signals. While Vp and mean acceleration (MA) correlated with dP/dt max ($r = 0.837$ and 0.811 , respectively) a better correlation ($r = 0.866$ $p < 0.001$) was found for $\frac{KVp^2}{T} + \frac{\text{pulse } P}{TC}$.

This method may prove useful in the non-invasive estimation of dP/dt max under differing clinical conditions, particularly if there are rapidly changing (beat to beat) variations in contractility.

Magnetic resonance imaging of atrioventricular septal defects in children correlates with echocardiographic, angiographic, and surgical findings

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Magnetic resonance (MR) imaging was performed in seven patients (age range 11 days–14 months) with atrioventricular septal defects (AVSD). Echocardiographic studies had previously been performed in all patients, and five subsequently had angiography. Three patients have since been surgically corrected. Associated defects present were Fallot's tetralogy in one case, and right atrial isomerism with pulmonary atresia in another. A 1.5 T whole body MR imaging system was used with patients sedated and positioned supine inside a 32 cm diameter head coil. Multiple ECG gated sections 5 mm thick were acquired using a spin echo sequence with echo time of 30 ms. A combination of standard and oblique imaging planes were used. The MR images were compared with the other investigations in order to assess the size of the ventricular component of the defect, the attachments of the atrio-

ventricular valve, and the left and right ventricular dimensions. MR predicted the size of the ventricular component of the defect in every case with full agreement with angiographic and surgical findings. In all cases MR demonstrated the defect in more detail than echocardiography. In four patients the attachments of the superior and inferior bridging leaflets to the ventricular septum were clearly shown. In this respect there was full agreement with those patients who had surgery. MR was an accurate method of determining ventricular dimensions. In one patient MR correctly predicted severe ventricular disproportion which was confirmed at operation.

MR imaging is capable of providing detailed morphology data in infants with AVSDs. This information is likely to be of value in the preoperative assessment of these patients.

Thrombin inhibition by heparin or hirudin decrease platelet thrombus deposition and vasospasm after arterial angioplasty

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To test the hypothesis that localised vasoconstriction after arterial injury is related to platelet deposition, the effects of heparin and recombinant hirudin (a more specific thrombin inhibitor than heparin without intrinsic vasodilating properties) were tested on platelet deposition and spasm following experimental angioplasty. After heparin (35 u/kg bolus + 35 u/kg/hour infusion, $n = 10$, or 250 u/kg + 250 u/kg/hour, $n = 9$) or hirudin (1 mg/kg + 1 mg/kg/hour, $n = 5$) pigs underwent bilateral carotid angioplasty (five inflations for 30 seconds to 6 atmospheres, 60 seconds apart). Vasoconstriction (1% luminal diameter narrowing immediately distal to the dilated segment) was assessed by computer assisted analysis of angiograms taken before and 1 minute after injury. The time course of spasm after injury was assessed by serial angiograms (1, 5, 15, 30, and 60 minutes after injury) in 11 animals. Platelet deposition ($\times 10^6/\text{cm}^2$ of deep arterial injury) was measured using indium III labelling. Platelet deposition in the low dose heparin group was 305 (77) and was less with high dose heparin (59 (18), $p < 0.002$) or hirudin (28 (8), $p < 0.001$). Mural thrombus occurred in 72% of deeply injured segments in the low dose heparin group, and occurred less often in the high dose heparin group (10% $p < 0.001$) or with hirudin (0%, $p < 0.001$). Vasoconstriction at 1 minute was positively correlated with platelet depo-

sition ($r = 0.32$, $p < 0.01$). Vasoconstriction at 1 minute was 49 (3)% in the low dose heparin group and was less after high dose heparin (26 (5)%, $p < 0.01$) or after hirudin (33 (5)%, $p < 0.02$). Vasoconstriction was most intense one minute after injury (37 (4)%) and almost absent at 60 minutes (15 (2)%, $p < 0.01$).

The results show that inhibition of thrombin by heparin or hirudin reduces thrombosis and vasoconstriction associated with arterial injury. These effects are related to their ability to inhibit thrombin induced platelet activation. The results underline the importance of platelets as mediators of vasospasm after arterial angioplasty.

Reduction in major morbidity and mortality by heparin in acute myocardial infarction

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About 5700 patients with suspected acute myocardial infarction (AMI) have been randomised in 20 trials of subcutaneous (sc) or intravenous (iv) heparin. Individually, these trials were too small to provide reliable estimates of treatment effects on major morbid events and death. An overview of the trials, however, in which results from individual studies were combined, provides strong evidence of beneficial effects. Overall, among all patients allocated heparin, the "typical" odds of death was 17% (7) lower ($2 p = 0.005$) than among those allocated control. Furthermore, treatment with heparin was associated with significant reductions in deep vein thrombosis (66% (7); $2 p < 0.001$), pulmonary embolus (54% (8); $2 p < 0.001$), reinfarction (22% (10); $2 p < 0.05$) and stroke (50% (16); $2 p < 0.005$). The effect of heparin on total stroke suggests that in these trials any increase in cerebral haemorrhage resulting from anticoagulation was outweighed by a reduction in cerebral infarction. The heparin regimen tested in about 90% of patients entailed doses of 20 000 IU or more daily, given subcutaneously in about half the patients.

In the UK and USA, such doses of sc or iv heparin are used only in a minority of patients with suspected AMI. Some physicians may wish to reconsider this policy in the light of the present results. Others may feel that further randomised evidence is needed about the effects of heparin in the current era of treatment with thrombolytic and antiplatelet agents.

Electrophysiological study of survivors outside hospital from ventricular arrhythmias unassociated with acute myocardial infarction

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We studied 32 survivors (25 men) of life threatening ventricular arrhythmias not due to acute myocardial infarction (MI) that occurred outside hospital. Mean age was 57 years (range 9–79). Electrophysiological study (EPS) included three programmed extra-stimuli in sinus rhythm and ventricular pacing drive rate of 100, 120, and 140 per minute (S4 protocol) from at least two right ventricular sites. Twenty patients had a previous history of MI. In 10 patients the initial documented rhythm was ventricular fibrillation (VF), in 12 ventricular tachycardia (VT), and in 10 VT deteriorated into VF. During EPS non-sustained VT was induced in nine patients, sustained VT in 15, and VF in both the survivors. Of patients with induced VT, 19 had cycle length < 300 msec. VT or VF was induced in 16 of 20 patients with left ventricular ejection fraction (EF) $\geq 30\%$, and in 10 of 12 patients with EF $< 30\%$ (no significant difference). During follow up (four weeks to 35 months) ventricular arrhythmias were suppressed by treatment for underlying heart disease and EPS directed treatment in 16 patients. In six patients serious VT recurred, and in two was due to poor drug compliance. Serious VT recurred in one of six patients with initial negative EPS. One death occurred during follow up, in one of six patients whose EPS induced VT could not be completely suppressed by drug treatment. Inducibility of VT/VF during EPS was not related to previous MI or whether documented prehospital rhythm was VF or VT.

We suggest that EPS in survivors of ventricular arrhythmias occurring outside hospital is of value in determining prognosis and treatment.

Rise in left atrial pressure does not limit exercise capacity in patients with hypertrophic cardiomyopathy

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The hypothesis that exercise capacity in hyper-

trophic cardiomyopathy (HCM) is limited by a rapid rise in left atrial pressure as a result of a systolic gradient or impaired diastolic function has not been tested. Twenty three patients, age 15–70 (mean 36) years, in whom exercise capacity was limited only by dyspnoea were selected. Patients with severe mitral regurgitation, pulmonary disease, or an inability to exercise for any reason other than dyspnoea or fatigue, were excluded. Pulmonary capillary wedge pressure (PCWP), maximal oxygen consumption (VO_2 max) and anaerobic threshold were measured during symptom limited treadmill exercise testing. VO_2 max was reduced ($28.1 (7.5) \text{ ml/kg/minute}$; normals >40) as was anaerobic threshold ($21.5 (6.1) \text{ ml/kg/minute}$; normals >30), even in 12 of 13 NYHA Class I patients. All patients stopped because of dyspnoea. Supine resting PCWP (mm Hg) was 15 (5). Erect PCWP rose from 5 (5) at rest to 24 (11) at peak exercise, and cardiac index (l/minute/m^2) from $2.4 (0.6)$ to $8.1 (2.1)$. VO_2 max and anaerobic threshold were related to peak cardiac index ($r = 0.65$, $p < 0.001$, and $r = 0.46$, $p = 0.03$, respectively) as well as the rise in cardiac index on exercise ($r = 0.68$, $p < 0.001$, and $r = 0.51$, $p = 0.016$, respectively) but not to resting cardiac index, resting and peak PCWP, the rise in PCWP on exercise, or PCWP at a submaximal oxygen consumption value of 15 ml/kg/minute .

These findings confirm previous reports of an abnormal rise in left atrial pressure but are not consistent with the hypothesis that raised left atrial pressure is the major determinant of exercise capacity in patients with HCM, and suggest that as in patients with chronic heart failure, other mechanisms should be considered.

Myocardial perfusion SPET scintigraphy with technetium 99 methoxy-isobutyl-isonitrile in coronary artery disease: comparison with thallium 201

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Technetium-99m MIBI (methoxy-isobutyl-isonitrile) has recently been introduced as a new radiopharmaceutical for myocardial perfusion scintigraphy. Labelled with $^{99}\text{Tc}^m$, it may be superior to the standard thallium ^{201} in the detection and localisation of coronary disease. Twenty nine patients (aged 41–72 years, mean 55 years) with established

coronary artery disease (CAD) (50% or greater diameter stenosis on coronary angiography in at least one vessel) were investigated. Stress and rest delayed studies were carried out with $^{99}\text{Tc}^m$ MIBI (370 MBq at peak stress and rest 24 hours or more later) and ^{201}Tl (74 MBq at peak stress) within seven days of first test. Each patient achieved identical rates of exercise on graded supine bicycle ergometer. Post stress (5–10 minutes of ^{201}Tl and one hour of $^{99}\text{Tc}^m$ MIBI injection) and delayed/rest SPET studies were performed in each case using IGE 400 AC/STARCAM and 400A STAR gamma camera computer system. Myocardial ischaemia (as expressed by reduced tracer uptake) was seen in 66 of 145 (46%) myocardial segments with ^{201}Tl and 70 of 145 (48%) segments with $^{99}\text{Tc}^m$ MIBI. Four segments showed normal uptake of ^{201}Tl but reduced uptake of $^{99}\text{Tc}^m$ MIBI while opposite was seen in two segments. Reversible or irreversible myocardial ischaemia as predicted by ^{201}Tl was present in 26 out of 29 patients (90%) whilst $^{99}\text{Tc}^m$ MIBI predicted disease in 28 out of 29 patients (95%). Both radiopharmaceuticals could accurately localise coronary lesions and their functional significance. The quality of the $^{99}\text{Tc}^m$ MIBI tomogram was similar or better than that using ^{201}Tl .

This study demonstrates the high sensitivity obtained with $^{99}\text{Tc}^m$ MIBI in the detection of coronary disease. It has the advantages of easier availability than ^{201}Tl , and exercise testing may be performed at a site remote from the nuclear imaging system. This will reduce the number of exercise tests needed in the investigation of coronary disease.

Magnetic resonance chemical shift imaging of human atheroma

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Magnetic resonance can show protruding atheromatous plaques either using conventional imaging or angiographic techniques, but chemical shift imaging also allows an assessment of the lipid content of a lesion. This is of considerable clinical importance because the ability to modify atheroma in a patient either pharmacologically or mechanically depends upon its composition.

Twelve necropsy specimens of human descending aorta and the aortas of two patients with documented atheroma were studied using a spin echo sequence to localise protruding lesions. The specimens were

maintained at 37°C and were distended at 80 mm Hg pressure. Chemical shift imaging was performed using the technique described by Dixon that produces maximum signal for a 50% mixture of lipid and water and no signal for either pure lipid or pure water. Since the specimens contained less than 50% lipid, the signal strength was proportional to lipid content, and the signal from atheroma was expressed as a proportion of that from extravascular fat. Calibration was performed using fat and water mixtures. After imaging the specimens were examined histologically using haematoxylin and eosin, elastic van Gieson, and oil red O fat stains. The lipid content of the plaques was scored as either absent, low, medium, or high, and the distribution of lipid within the plaque and between intima and media was noted. Lipid content assessed by magnetic resonance ranged from 8% to 50% compared with extravascular fat. There was good agreement with the histological findings and all but one plaque with signal intensity over 25% had high lipid content histologically. The distribution of lipid within the plaques also agreed with histology and intimal lipid was particularly prominent in the majority. In one patient, atheroma in the descending aorta was shown to have a high lipid content and in the other, a low lipid content. Histological confirmation was not possible.

Magnetic resonance chemical shift imaging provides a method of assessing the lipid content of atheromatous plaques. Validation in vivo is more difficult than in vitro but results can be obtained. The usefulness of the technique in routine clinical practice remains to be established.

Impact of colour Doppler flow mapping on the assessment of congenital heart disease

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The role of cardiac catheterisation in the investigation of congenital heart disease is reassessed in the light of the increased ability of non invasive techniques with the development of colour Doppler flow mapping (CDFM) which enhances the ability of echocardiography to demonstrate intracardiac lesions.

During a seven month period 142 patients underwent surgery (59 having had previous catheterisation) and 111 catheterisation (26 for interventional procedures). In those undergoing

catheterisation full echocardiographic and spectral and CDFM studies were performed, and a form stating the exact non-invasive diagnosis with assessment of the haemodynamic measurements (particularly shunt size and pulmonary pressure) was completed before the procedure, and the contribution of catheterisation to the final diagnosis assessed. Of those catheterised there was no major discrepancy in the assessment of the diagnosis, shunt size, or the severity of obstructive lesions. Ultrasound was unable to provide sufficient detail to permit surgical intervention in those with complex venous abnormalities, coronary artery fistula, or distorted pulmonary arteries. In three cases venous abnormalities not commented on before catheterisation were recognised afterwards. Little additional information was obtained from catheterisation in 50% of patients but the decision on the need for surgery would not necessarily have been the same had it not been undertaken.

CDFM adds to the diagnostic ability of imaging and spectral Doppler in the assessment of congenital heart disease and will further reduce the need for catheterisation before surgery.

Prediction of outcome after acute uncomplicated myocardial infarction: a study of 394 patients with five years follow up

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Three hundred and ninety four consecutive patients were studied prospectively after an acute uncomplicated myocardial infarction by predischARGE maximal treadmill exercise testing and coronary angiography at six weeks. Logistic regression analysis was used to produce a simple predictive index that could be applied at the end of the exercise test to predict the coronary anatomy and the therapeutic outcome in these patients. Four models were constructed out of 11 variables, with age as a continuous variable. The best model for predicting coronary anatomy was found to consist of angina, exercise time, maximal ST segment depression, and myocardial infarction site. Coronary anatomy then added most to the combined predictive power of exercise time and ST segment depression, which together dictated the outcome. The sensitivity and specificity of the exercise tests were 94 and 92%, respectively. Based on this model 214 patients required coronary bypass surgery during the follow up period. Of these 141 patients had inferior, 63 had anterior, and 10 had

posterior infarction, compared with 75, 101, and 4 respectively in the medically treated group of patients. Sixteen patients underwent additional surgical procedures during coronary bypass surgery and the operative mortality was 3%. An analysis of cross tabulations of the exercise variable in this model provided a summary of prediction probabilities within various subgroups of patients.

Of patients with exercise time of ≤ 6 min and ≤ 1.5 mm horizontal or downsloping ST segment depression, 68% (60/88) required surgical treatment compared with only 25% (32/125) of patients with an exercise time of > 6 min and < 1.5 mm ST segment depression. ST segment depression of > 1.5 mm did not add to the predictive power of this model.

Right ventricular dysfunction enhances mortality after myocardial infarction

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After myocardial infarction, left ventricular ejection fraction is known to predict mortality, but the predictive value of right ventricular dysfunction is less clear. Right and left ventricular ejection fraction (RVEF and LVEF) were measured in 81 consecutive patients with myocardial infarction at one day (EF 1), three days (EF 2), before discharge (EF 3), and at a mean of 16 months later (EF 4) using gated blood pool ventriculography. In 36 patients with anterior myocardial infarction mean LVEF did not alter significantly throughout the study period but RVEF deteriorated from day 1—RVEF 36.8 (9.9)%, to 16 months 32.4 (7)%—($p < 0.01$). For the 45 patients with inferior myocardial infarction, mean left ventricular function deteriorated slightly in hospital and subsequently improved by follow up (LVEF 1 31.3 (8)%, and LVEF 4 34.1 (9.9)%, $p < 0.02$) but right ventricular function did not change. Mortality was 31% (11/36) for anterior infarcts and 16% (7/45) for inferior infarction. If a LVEF $< 30\%$ was considered abnormal, 33% (16/45) were dead at follow up compared with 6% (2/33) of those with preserved left ventricular function. With right ventricular dysfunction (RVED $< 35\%$) 25% were dead at follow up, and 19% of those with preserved right ventricular function had died. Twenty nine patients had both right and left ventricular dysfunction, however, and the mortality was 41% (12/29) compared with 22% (4/18) in those with only left ventricular dysfunction.

In conclusion, this suggests that after myocardial infarction right ventricular dysfunction enhances the risk of mortality in patients with left ventricular dysfunction.

Diagnostic importance of reciprocal ST segment depression in acute myocardial infarction

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The interpretation of reciprocal ST segment depression (RSTD) in acute myocardial infarction (AMI) remains controversial. It might represent acute ischaemia of the underlying myocardial segment. One hundred and forty two patients with a classical AMI underwent early submaximal exercise tests (SM-ET). All patients with positive SM-ET ($n = 76$) and one third of those with negative SM-ET ($n = 30$), chosen at random, had coronary angiograms shortly afterwards. RSTD was observed in 65% of patients with inferior MI and 57% of those with anterior MI. Of the 52 patients with RSTD who had coronary angiography, 33 had significant lesions of the coronary artery that subserves the RSTD territory (63%), while of the 46 patients with positive SM-ET, 31 had comparable lesions of the coronary artery that supplies the ischaemic territory (67%). The incidence of multivessel coronary artery disease in the two groups was 79% and 76%, respectively.

This study has shown that RSTD is a common electrocardiographic finding in acute myocardial infarction. It is associated with stenosis of the RSTD subserving coronary artery in nearly two thirds of the patients, and with multivessel coronary artery disease in almost four fifths. RSTD is as good as the SM-ET at predicting the anatomy of the underlying coronary artery disease.

Prognostic value of heart rate variability after myocardial infarction

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The prognostic value of heart rate variability was studied in 54 patients within two weeks of infarction. Ten patients either died or developed ventricular tachycardia (VT), and five had non-fatal rein-

farctions during a mean follow up of 13 months (median 8 months). Computer analysis of a standard 24 hour tape permitted identification of every interval between normal beats; a frequency distribution was generated and the mean RR interval (mean RR), the standard deviation of RR intervals (SD RR) and the range of RR intervals comprising the principal frequency distribution peak (range RR) were evaluated. There was a significant difference between the mean RR interval and range RR when patients with an uncomplicated course and those with death or VT were compared (mean RR $0.884 (0.10) \pm 0.69 (0.09)$ s, $p < 0.0001$; range RR $0.92 (0.23) \pm 0.55 (0.25)$ s, $p < 0.0001$). There was, however, no significant difference between the standard deviation of RR intervals in the two groups. Stepwise multiple regression analysis showed that of all the variables examined, including mean RR, range RR, SD RR, ectopic frequency, Lown grade and the occurrence of complications in hospital, the most important predictor of death or VT was range RR. There was a weak correlation ($p < 0.02$) between range RR and left ventricular function assessed by cine-ventriculography or gated blood pool scan; range RR and ejection fraction had independent prognostic value. Treatment with β blockers did not affect range RR, though mean RR was significantly greater in those 15 patients on β blockers and none of the patients were on antiarrhythmic therapy.

In conclusion, range RR is a superior prognostic index to SD RR in the prediction of death or VT after infarction, and provides independent prognostic information in addition to clinical assessment and other 24 hour tape variables, including heart rate.

Characteristics and prognosis of non-Q wave myocardial infarction

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Survivors of non-Q wave myocardial infarction are reputed to have a comparatively high risk of subsequent cardiac events including sudden death, re-infarction and angina. The frequency of non-Q wave infarction and subsequent prognosis were therefore investigated in 337 survivors of definite myocardial infarction. The results of predischARGE submaximal exercise testing were available in all patients, coronary angiography in 109 patients, and all were followed for 12 months. Non-Q wave infarction

occurred in 80 patients (24%) of whom two died (2.5%), seven reinfarcted (9%), and 32 developed angina (40%) during the 12 month follow up. Of those with Q wave infarction, 12 (5%) died, 21 (8%) reinfarcted, and 99 (39%) developed angina. Positive predischARGE exercise tests were recorded in 47 (59%) patients with non-Q wave infarction and 138 (54%) patients with Q wave infarction. A positive test predicted cardiac events with similar frequency in non-Q wave infarction (73% subsequent events) and Q wave infarction (83% subsequent events). The ratio of silent to painful predischARGE ischaemia during submaximal exercise testing was identical in both groups. Coronary angiography was available in 109 patients, 84 with Q wave and 25 patients with non-Q wave infarction. Single vessel disease was found in 12 of 25 (48%) with non Q wave infarction and 25 of 84 (30%) with Q wave infarction. Double and triple vessel disease were equally distributed in the remaining patients.

Thus non-Q wave infarction was seen in 24% of infarct survivors and had a similar clinical outcome in the ensuing 12 months. This is supported by identical predischARGE exercise test characteristics and a similar distribution of coronary artery disease.

Breathlessness, lung function, and risk of heart attack

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Diminished pulmonary vital capacity and dyspnoea are recognised as consequences of advanced heart disease. Their relevance in earlier stages of heart disease is less well documented. In a prospective study of 7735 British men aged 40–59 years and followed up for 7.5 years, men with moderate or severe breathlessness had a greater than two fold risk of suffering major ischaemic heart disease (IHD) compared with men with no evidence of breathlessness. After adjustment for other risk factors, including cigarette smoking, the relative risk remained two fold. Men in the lowest fifth of the FEV₁ distribution also had a two fold risk of IHD compared with men in the highest fifth, after similar adjustment. Reduced lung volume rather than obstruction seemed to be the determinant of risk as FVC exhibited a similar association with FEV₁, while FEV₁ to FVC% was less strongly associated with risk. The role of breathlessness as a risk factor for new IHD was partly explained by its strong association with pre-existing but usually undiagnosed IHD. Both a reduced FEV₁ and breathlessness,

however, were associated with raised risk of major IHD events even in men without any evidence of IHD at screening.

The incidence of angina during the five years after screening was strongly associated with breathlessness grade at screening, suggesting that breathlessness is an early indicator of IHD in the absence of other symptoms.

One hundred and thirty three cases of spontaneous atrial flutter: electrophysiological characteristics and factors affecting successful conversion

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One hundred and thirty three unselected consecutive cases of atrial flutter were studied in 114 patients (86 men, 28 women, mean age 54, range 18–79). In 118 cases the flutter was of the common type. Duration of flutter ranged from 10 minutes to 16 years (median four days). The mean (SD) atrial cycle length during flutter was 223 (35) ms. Drug treatment included digoxin ($n = 40$) and amiodarone ($n = 13$). Atrial mapping was performed in 75 cases (424 sites) and showed predominantly downward activation of the lateral right atrium and upward activation of the atrial septum in common flutter. Sites exhibiting a reset response to atrial programmed extrastimuli (APE) were most commonly found in the low lateral, septal, and posterior right atrium, indicating preferential inclusion of these sites in a reentry circuit. Conversion was not attempted in 17 cases (12 proceeded to catheter ablation, five had areas of coexisting atrial fibrillation (AF)). In the remaining 116, 1–4 APEs resulted in conversion to sinus rhythm (SR) in 23 cases (20%) and to AF in five (4%). In 82 cases, conversion was then attempted using a single long constant current pulse (atrioversion). SR was achieved in 36 cases (44%), and AF in 30 (37%). In 29 cases who had failed either one or both of the above attempts, rapid atrial overdrive pacing (RAP) achieved SR in 12 cases (41%), and AF in 13 (48%). Overall, 72 cases (62%) were converted to SR and 39 (34%) to AF (12 reverted spontaneously to SR in less than 24 hours). Five cases (4%) remained in flutter.

Factors significantly improving successful conversion included coronary artery bypass grafting in the previous month (SR in 86%), congenital heart disease (SR in 89%), and stimulation at a site

exhibiting reset. Thus aetiology and detailed atrial mapping may significantly affect successful conversion.

Verapamil or adenosine for supraventricular tachycardia

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The place of intravenous verapamil as the treatment of choice for supraventricular tachycardia (SVT) has recently been challenged by the use of intravenous adenosine, a rapidly metabolised naturally occurring compound. We have reviewed 105 spontaneous episodes of paroxysmal SVT in 38 patients (aged 16 to 79 years; mean 44 years) treated acutely with either agent. Verapamil was given to 22 patients during 65 episodes of SVT, and adenosine to 21 patients on 40 occasions. Five patients received both compounds. Verapamil, 3 to 30 mg (mean 7.7 mg), restored sinus rhythm in all 22 patients, in 57 of 65 episodes (88%), within 40 minutes of administration. In four patients verapamil (5 to 25 mg) failed to terminate SVT in 8 of 22 episodes. Hypotension (systolic BP < 90 mm Hg) occurred after verapamil in seven episodes (10%) in four patients, requiring emergency DC cardioversion on three occasions. Arrhythmia recurred following verapamil within one hour in only one patient and within 12 hours in two. Adenosine was administered by incremental doses, from 2.5 to 25 mg (mean effective dose 10.4 mg). Sinus rhythm was restored in all 21 patients in 38 of 40 episodes (95%) within one minute of administration. In one patient SVT persisted despite adenosine (15 and 20 mg) in two of 14 episodes. Early recurrence of SVT (within 10 minutes) occurred in eight patients (36%). No haemodynamic deterioration was observed after adenosine, but minor transient side effects were common (77%).

In conclusion, both verapamil and adenosine are highly effective in the treatment of SVT. Adenosine acts more rapidly and is safer, but its effect is short lived and arrhythmias may recur.

Comparative efficacy and safety of adenosine, lignocaine, disopyramide, flecainide, and sotalol in the termination of ventricular tachycardia

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Drug termination is frequently used in the acute management of ventricular tachycardia. The comparative merits of the various drugs available are not known. In this study drugs were given intravenously as bolus doses (adenosine and sotalol) or infusions (disopyramide, flecainide, and sotalol) during induced, sustained, haemodynamically stable ventricular tachycardia in serial trials. Tachycardia was terminated by programmed stimulation if it continued 10 minutes after the end of drug administration. Twenty four patients underwent 105 trials with termination of ventricular tachycardia in 35 trials by the drug. In six patients no drug terminated ventricular tachycardia. Adenosine did not terminate ventricular tachycardia in any patient (so acted as a control), lignocaine in 7/23 patients, disopyramide in 12/24 patients, flecainide in 11/20 patients, and sotalol in 5/15 patients. If the ventricular tachycardia was not terminated by flecainide, then in only 3/9 patients was it terminated by another drug. This was much lower than seen with disopyramide (6/12), lignocaine (10/17) and sotalol (6/10). Serious adverse effects during ventricular tachycardia were seen in 5/20 patients with flecainide (4 proarrhythmic, 1 haemodynamic), in 2/15 patients with sotalol (both haemodynamic), and in 1/24 patients with disopyramide (proarrhythmic), but were not seen with lignocaine or adenosine.

In conclusion, flecainide is the most effective drug at terminating ventricular tachycardia but has the most adverse effects. Lignocaine was both significantly safer and less effective ($p < 0.05$). Disopyramide and sotalol were more effective but had more side effects than lignocaine and were safer but less effective than flecainide.

Efficacy of flecainide for atrial arrhythmias after open heart surgery

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The antiarrhythmic effects of intravenous flecainide and intravenous digoxin were assessed in 29 patients (26 men aged 43 to 73 years, mean 60) who developed atrial arrhythmias in the first 96 hours after open heart surgery. Twenty seven had AF and two had atrial flutter. Patients were entered in to the study only if the arrhythmia was observed for at least 15 minutes with a ventricular rate of more than 120/minute. Patients were randomised to flecainide or digoxin. Flecainide was given as a bolus of 1 mg/kg over 10 minutes followed by infusion of 1.5 mg/kg/hour for one hour followed by infusion of

0.25 mg/kg/hour for the rest of the 24 hour study period. Digoxin was given as three bolus doses of 0.5 mg followed after six hours by 0.25 mg and after another six hours by 0.25 mg. In both groups, verapamil was subsequently given after 45 minutes if no reversion to sinus rhythm or adequate ventricular rate control ($< 100/\text{minute}$) was achieved. Fifteen patients were given flecainide, five of whom required verapamil. Fourteen patients were given digoxin, 13 of whom required verapamil. The antiarrhythmic efficacy was assessed by 24 hour Holter monitoring and 15 second rhythm strips taken at 1, 2, 3, 6, 12, and 24 hours. After flecainide arrhythmia terminated in 9/15 within one hour and did not recur during the 24 hour study period. In 1/15 arrhythmia persisted with a controlled ventricular rate that was maintained throughout the study period. Flecainide with verapamil terminated arrhythmia in 1/15, controlled the ventricular rate in 1/15, and failed to control arrhythmia in 3/15. Digoxin alone failed to terminate arrhythmia in all 14 and controlled the ventricular rate in only 1/14 ($p = 0.001$). Digoxin with verapamil terminated arrhythmia in 1/14, controlled the ventricular rate in 1/14 and failed to control arrhythmia in 11/14. None of the patients in the two groups had major side effects.

We conclude that intravenous flecainide is more effective than conventional drug treatment for post-operative atrial arrhythmias.

Prediction of life threatening arrhythmias in hypertrophic cardiomyopathy using high gain, signal averaged, electrocardiography

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The prediction and prevention of sudden death remains a major objective in the management of hypertrophic cardiomyopathy (HCM). We have investigated the value of late potentials (LP) detected using high gain, signal averaged electrocardiography in predicting arrhythmias in 31 HCM patients. Maximum echocardiographic wall thickness was 15–29 mm, median 22 mm; 15 patients were taking amiodarone (median dose, 200 mg/day); 12 of the patients were young (< 25 years), and of these three had been resuscitated having gone into ventricular fibrillation (VF) when not in hospital. All 31 patients had 48 hour electrocardiographic monitoring; eight had non-sustained ventricular tachycardia (VT), and one had sustained VT. None of the three patients with a history of VF had arrhythmias on electrocardiographic monitoring. LP were detected using Simson's method; patients with bundle branch block were

excluded, and a prolonged filtered QRS was not considered positive for LP if the surface QRS was > 120 ms. LP were present in 7/31 (23%). There was no difference between the incidence of LP in those who were and were not taking amiodarone, and there was no correlation with the degree of echocardiographic left ventricular hypertrophy. Of the four patients with a history of life threatening arrhythmias, three (the one with sustained VT and two of the three with VF) had late potentials. The sensitivity for the prediction of life threatening arrhythmias by LP was thus 75%, the specificity 85%, and the positive predictive accuracy 43%. Of the nine patients with non-sustained VT four had LP compared with 3/22 without VT ($p < 0.05$). All eight patients with non-sustained VT have had a benign course.

In conclusion, the presence of LP in patients with HCM correlates both with the occurrence of life threatening arrhythmias and non-sustained VT, a known prognostic marker in HCM. Signal averaged electrocardiography may therefore be of value in the assessment of the risk of sudden death in HCM, especially in the younger age group, where currently no prognostic indicator exists.

Hospital mortality of ventricular tachycardia and fibrillation

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Factors influencing hospital mortality of ventricular tachycardia (VT) and/or ventricular fibrillation (VF) were prospectively investigated in 124 consecutive patients between January and June 1988. Seventy seven (62%) were men, and 102 (82%) had ischaemic heart disease. Fifty five had had acute myocardial infarctions (MI). Age, sex, previous history of VT/VF, aetiology, site of MI, number of previous MIs, drug history, and NYHA functional state were recorded. Seventy three patients (59%) survived to leave hospital. The following were statistically significantly associated with hospital mortality by univariate analysis: age > 60 ($p < 0.05$), female sex ($p < 0.01$), first episode of VT/VF ($p < 0.01$), anterior MI ($p < 0.01$), use of inotropes ($p < 0.01$), NYHA 3 or 4 ($p < 0.001$). Other features showed no significant correlation with outcome. Hospital mortality rose in association with increasing numbers of "risk" factors: hospital mortality was 4.7% when no factor or one alone was present, 30.6% when two or three factors were present, 63.6% when four factors were present, and

94.5% when five or six factors were present.

This study shows that VT or VF, or both, carry an appreciable hospital mortality (41%); several clinical features correlate with the risk of death. Previous history of VT/VF was not associated with an increased hospital mortality. The natural history of and risk factors for VT and VF whether or not in the context of acute ischaemia are poorly documented.

Role of transoesophageal echocardiography in the diagnosis of aortic dissection: a cooperative multicentre trial

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Transoesophageal echocardiography (TEE) can view the entire thoracic aorta and thus could provide all the required diagnostic information about the type and complications of aortic dissection. In a multicentre cooperative study both the sensitivity and specificity of this method were tested in 181 patients with proved (99) or excluded (82) aortic dissection. The echocardiographic findings were compared with computed tomographic (CT), angiographic, and surgical or necropsy findings, or both, in 75 patients; with CT and angiography in 89 patients; and with surgical findings alone in 17 patients. In the 164 patients with correlative angiographic, CT and TEE findings, TEE correctly defined an aortic dissection in 81/82 patients. One false negative result occurred in a type II dissection. In addition there were two false positive diagnoses. In comparison, CT gave false negative results in seven patients and no false positive results. Aortography gave false positive results in three patients and false negatives in nine. The sensitivity and specificity of TEE were 99% and 98%, respectively, with a positive and negative predictive accuracy of 98% and 99%. For CT the sensitivity measured 83% and specificity 100% with (+) and (-) predictive accuracies of 100% and 86%, respectively. For aortography the comparable sensitivity and specificities were 80% and 94%, respectively, and the (+) and (-) predictive accuracy 96% and 84%. Aortic dissection was reliably differentiated from aortic aneurysm and aortic dilatation. Colour flow imaging clearly defined the

abnormal flow patterns in the true and false lumens and the site of the proximal entry point(s).

We conclude that TEE is the diagnostic technique of choice in aortic dissection.

An evaluation of homovital aortic valve homografts

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Between January 1980 and April 1988, 99 homovital aortic valves, obtained under sterile conditions at the time of cardiac transplantation, were used for aortic valve replacement (61 patients) or aortic valve and root replacement (38 patients). The valves were kept at 4°C until used 1.5 to 72 hours later. ABO compatibility was achieved in 63 (63%) patients. Twenty four patients were immunosuppressed with azathioprine and prednisolone for three months. Additional procedures were performed in 21 patients (21%). There were two (2%) early deaths, both in patients with additional procedures, and four (4%) late deaths during a follow up period ranging from 1 to 99 months (mean 22.5 months). The five year actuarial survival for patients with isolated aortic valve replacement was 95%. Valves failed in three patients and this was related to endocarditis in two patients (30 and 48 months after operation), and degeneration eight years postoperatively in one patient. All three patients were reoperated on successfully. The cumulative probability of freedom from endocarditis and valve failure was 94% at 6 years.

It is concluded that the medium term results of homovital homografts are good, with no evidence of early rejection.

Is there a limit to operability in aortic stenosis?

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It has been argued that elderly patients with aortic stenosis, and those with poor left ventricular function, should be considered for valve dilatation as they are at high risk from surgery. To investigate this assumption, a retrospective study was made of all 74 patients who underwent valve replacement for pure aortic stenosis, under the care of a single surgeon,

between January 1982 and December 1987. This included patients having simultaneous coronary artery surgery. There were 46 men and 32 women. Median age was 66 years (range 29–86). The median aortic gradient was 80 mm Hg (range 20–140). Poor left ventricular function was assessed by (a) presence of clinical left ventricular failure, (b) poor left ventricular function at cardiac catheter, (c) left ventricular end diastolic pressure over 25 mm Hg, and (d) left ventricular ejection fraction under 30% (MUGA). All four signs were not available for all patients. Ten patients were classed as having poor left ventricular function based on the presence of two or more criteria. There was no significant difference in age or aortic gradients between the good and poor function groups. Inotropic support was required by 2/64 of the good LV group compared with 2/10 of the poor group. Median hospital stay was 10 days (range 6–32) for the good LV group and 8.5 days (range 6–10) for the poor group, ($p = 0.5$, Mann-Whitney U test). Median follow up was three years. No peri-operative deaths occurred in either group.

We conclude that neither age nor poor left ventricular function need be a deterrent to surgery in aortic stenosis.

What is normal function of an artificial valve? A colour and continuous wave Doppler assessment

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To evaluate Doppler characteristics of normal artificial valves we studied 335 patients with 368 prostheses; 179 were in the aortic position (AVR) (98 Starr-Edwards (SE), 50 Björk-Shiley (BS), 7 Duromedics (DM), 12 Mitraflow (MF), 14 Hancock-Pericardial (HP) and 8 Carpentier-Edwards (CE)) and 189 in the mitral position (MVR) (116 SE, 43 BS, 3 DM, 12 MF, 8 HP and 7 CE). Peak flow velocities (m/s) and the derived transvalvular pressure gradients (mm Hg) were measured; for MVR pressure half time (m/sec) was also calculated. Prosthetic valve regurgitation was assessed using colour and continuous wave Doppler. The average pressure gradients were significantly higher ($p < 0.01$) in mechanical AVR (SE = 29 (15), BS = 31 (13), and DM = 18 (13)) than in bioprostheses (MF = 14 (9), HP = 17 (8), and CE = 19 (8)). Pressure gradients in mechanical MVR (SE = 10 (4), BS = 9 (4), and DM = 13 (2)) were not significantly higher than in bioprostheses (MF = 8

(3), HP 9 (3), and CE 9 (4)). Pressure half times were similar in mechanical (SE = 96 (27), BS = 87 (26), and DM = 75 (5)), and Bioprosthetic MVR (MF = 80 (17), HP = 88 (14), and CE = 95 (7)). Mild regurgitant flow was noted in 121/368 (32.9%) artificial valves. At repeat Doppler examination 3–20 months (mean 8) after the first postoperative study, the same regurgitant flow was present in 27/32 (84.4%) patients, whereas it became severe in 5/32 (16.7%) consistently with valve dysfunction.

Doppler echocardiography can determine haemodynamic characteristics for different types of artificial valves. Mild regurgitant flow should not be considered as a sign of prosthetic valve dysfunction and its early recognition is essential for the long term follow up.

Sympathetic neurohormonal response to dynamic exercise early after orthotopic cardiac transplantation

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We investigated the sympathetic neurohormonal response to dynamic exercise of seven healthy male orthotopic transplant recipients, mean age 35.4 (range 18–61) years, six (range 3–11) months after transplantation. They were compared with seven normal subjects mean age 35.1 (range 23–58) years. The subjects performed progressive dynamic exercise on a cycle ergometer. Blood samples were obtained from an indwelling venous cannula in a peripheral vein. Noradrenaline and adrenaline concentrations were measured by high performance liquid chromatography using electrochemical detection. All results are quoted as mean values (SD). Before exercise noradrenaline concentrations were 3.95 (1.6) nM in the transplant recipients and 2.9 (0.6) nM in the normal subjects. Noradrenaline concentrations were 4.8 (1.7) and 2.8 (0.9) nM, respectively, at 30 watts and 6.2 (1.7) and 3.8 (1.9) nM, respectively at 70 watts. Analysis of variance for repeated measures showed a significant difference between the noradrenaline concentrations in the two groups ($p < 0.05$), a significant increase in noradrenaline concentrations with exercise ($p < 0.001$), and a trend for a difference in the way noradrenaline increased with exercise ($p = 0.06$). The adrenaline concentrations at rest were 0.27 (0.12) nM in the transplant recipients and 0.36 (0.15) nM in the normal subjects. At 30 watts the concentrations were 0.33 (0.2) and 0.36 (0.17) nM, respectively, and at 70 watts 0.38 (0.3) and 0.45 (0.13) nM, respectively. Analysis of variance showed that adrenaline concen-

trations increased with exercise ($p < 0.05$) but there was no significant difference between the 2 groups. At maximum exercise noradrenaline concentrations were 15.3 (9) nM in transplant recipients and 12 (4) nM in the normals ($p = NS$), and adrenaline concentrations were 1.1 (0.9) and 1.9 (0.7) nM, respectively ($p = NS$).

This study has shown increased sympathetic activity in the transplant recipients before and during exercise.

Colour flow mapping as intraoperative angiography in ventricular septal defects: advantages and pitfalls?

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Fifty one patients undergoing surgical repair of one or more ventricular septal defects (VSD) were studied before and after cardiopulmonary bypass using an epicardial intraoperative technique to determine whether a combination of cross sectional imaging, contrast echocardiography, and colour flow imaging (CFI) could reliably predict (a) successful VSD closure, (b) the presence of further unsuspected VSDs, or (c) any resultant complications. Cross sectional imaging alone detected a minor degree of patch dehiscence in one patient. CFI after bypass showed immediate, well localised, trans patch or peripatch VSD jets in 26/51 patients (multiple jets 16/26). In none of these patients did contrast echocardiography suggest an important interventricular shunt. Early and late postoperative studies showed the disappearance of the narrow jets in 24/26 patients with "VSD closure" almost invariably occurring >6 hours after bypass. In a further four patients broad extensive CFI VSD transpatch or peripatch jets were immediately identified in all of whom contrast echocardiography suggested a small but important interventricular shunt. In none of these cases was bypass recommended as the defect appeared small. After bypass, further important distal VSDs (undetected by preoperative angiography) were noted in two patients, and bypass was recommended to effect closure. Late patch dehiscence (that is, >6 hours after bypass) was clearly defined in a further two patients.

We conclude that a combination of cross sectional imaging, contrast echocardiography, and colour flow imaging can provide the surgeon with a remarkably accurate intraoperative monitoring technique that can both confirm defective closure and exclude the presence of important residual VSDs.

Correspondence

Pitfalls and limitations in the use of impedance cardiography

Sir,

Technical improvements, method standardisation, and a better understanding of the limitations of transthoracic differentiated impedance cardiography have contributed to a recent resurgence of interest in the use of this technique as a non-invasive tool for the continuous monitoring of cardiac performance in man. We compliment Dr S A Smith and his colleagues on their interesting data (1988;59:292-8) but we are concerned that the well documented lack of accuracy of a specific electrical bioimpedance cardiograph (BoMed NCCOM3), which uses new and not well-defined techniques and mathematical procedures, might result in a general rejection of this method.

The accuracy of impedance cardiography is indeed limited; none the less, the technique is useful for the assessment of within subject changes of cardiac performance.^{1,2} The following additional limitations are too often ignored or underestimated: (a) the bioimpedance method merely offers "estimates" or "equivalents" of stroke volume; (b) the equations used to calculate these estimates are based on (over) simplified physiological assumptions³; (c) analysis of the impedance signals is often difficult, if not impossible, if a high quality phonocardiographic tracing does not detect aortic closure⁴; and (d) physiological, pathological, or drug induced distortions of the impedance signals by small amplitude high velocity presystolic impedance changes⁵ may invalidate the standard approach to the analysis of the signals.

Careful graphical analysis, manual or computerised, of the various tracings therefore remains essential for validity. Because this approach is tedious and time consuming, "simplified" techniques have been developed. The equipment assessed in the paper by Smith *et al* is a negative example of this approach. This equipment can indeed be criticised on many accounts: (a) it uses its own equation to estimate stroke volume, unlike the standard method of Kubicek *et al*⁶ and this equation does not accord with this standard,⁷ (b) it does not use a phonocardiogram as a reference for the analysis of the impedance signals, and (c) because it is designed as a "blind box" (that is, without analogue signal display) it does not allow the assessment of signal quality for distortion.

The conclusions of Smith *et al* therefore are not surprising; but it would be inappropriate for them to lead to the general rejection of impedance cardiography.

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This letter was shown to one of the authors, who replies as follows:

Sir,

We are grateful to Dr de Mey and Dr Belz for their interesting and constructive comments. In our paper we did not propose, nor did we intend to imply, that the technique of impedance cardiography should be "generally rejected" simply because of the poor results obtained with the BoMed NCCOM3. Indeed we accept that the technique may possibly provide useful semiquantitative information about stroke volume if operated within the constraints so clearly outlined by our West German colleagues.

However, we believe most of the published reports that at first sight seem to confirm the validity of impedance cardiography may require critical reappraisal. The main problem is that the cardiac output of any individual is related to his body size and heart rate. The empirical formulas used in impedance cardiography were designed to determine stroke volume and they include variables related to the subject's size (the base impedance and thoracic length). Most of the published studies have compared measurements of cardiac output obtained by impedance techniques with another measure of car-

diac output: such an approach will inevitably show a correlation. We believe that any critical analysis of impedance cardiography must remove the effects of heart rate and body size by examining stroke volume index. Such studies have been few and, in general, they have failed to confirm the validity of impedance methods.^{1,2} (Despite its title reference 2 does not confirm the validity of the technique.)

Clearly, further research is needed before impedance measurement of cardiac output can be accepted as a viable alternative to invasive methods.

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Notices

British Cardiac Society

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts will be 6 January 1989.

Thoracic and cardiovascular surgery and extracorporeal technology

The Annual Meeting of The Scandinavian Association for Thoracic and Cardiovascular Surgery and The Scandinavian Society for Extracorporeal Technology will take place in Aarhus on 13 to 16 September 1989. Further information from Secretary of the Congress Committee SATCVS/SCANSECT, Dr Chr Mouritzen, Department of Thoracic and Cardiovascular Surgery, Skejby Sygehus-Aarhus University Hospital, DK-8200 Aarhus N, Denmark.

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- 31 Balcon R, Brooks N, Layton C. Correlation of heart rate/ST slope and coronary angiographic findings. *Br Heart J* 1984; 52: 304-8.

Chapter in book:

- 28 Schiebler GL, Van Mierop LHS, Krovetz LJ. Diseases of the tricuspid valve. In: Moss AJ, Adams F, eds. *Heart disease in infants, children and adolescents*. Baltimore: Williams and Wilkins, 1968: 134-9.

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- 36 Feigenbaum H. *Echocardiography*. 3rd ed. Philadelphia: Lea and Febiger, 1981: 549-63.

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Review

Doppler colour flow mapping: technology in search of an application?

MARK J MONAGHAN, PETER MILLS

From King's College Hospital and The London Hospital, London

SUMMARY Although Doppler colour flow mapping may considerably reduce the need for conventional pulsed Doppler examination, quantitative flow measurements (particularly by continuous wave Doppler) are still essential in the evaluation of many conditions such as aortic stenosis. Doppler colour flow mapping is an important addition to the accurate non-invasive evaluation of several haemodynamic disorders of the heart and, as the technology improves, the range of applications will undoubtedly increase. Any technique that provides additional diagnostic information, makes an examination easier and quicker to perform, and at the same time provides data in a more comprehensible format has surely found a niche.

Since commercial colour flow mapping became available early in 1984, many have questioned its additional value over existing conventional Doppler echocardiography techniques. This scepticism has been fuelled by the knowledge that, unlike conventional echo and Doppler technology which evolved in university research departments, colour flow mapping was mainly developed by manufacturers before its likely clinical benefit was known. Colour flow mapping adds approximately £30,000 to the cost of an echo/Doppler instrument—the price of a small, conventional echo machine. The undoubted visual appeal of colour flow mapping must not be allowed to overshadow a consideration of its cost effectiveness.

The technology

The mean velocity and direction of blood flow in the scan plane are colour coded and these data are superimposed in real time on to the cross sectional ultrasound image to produce a spatially oriented map of blood flow. This can be correlated with the anatomical information from the conventional ultrasound image. The colour coded data on blood flow may also be superimposed on to an M mode

ultrasound recording enabling flow to be temporally correlated with mechanical intracardiac events. By convention, blood flow away from the transducer is coloured blue with an increase in brightness or change in hue for the higher velocities. Flow towards the transducer is displayed as red with higher velocities being registered by increasing brightness or changing hue through to yellow. The exact colour system depends both on the map selected and the instrument used.

The technique uses a modification of pulsed Doppler technology—autocorrelation—to acquire data on mean blood velocity and direction down a selected number of image scan lines.¹ The number of data points or sample volumes on each line, and hence the axial resolution of the instrument, can vary from under 100 to over 400 depending on the manufacturer. Figure 1 shows the autocorrelation principle.

Each line of Doppler data must be sampled several consecutive times to obtain data on flow and an image that are reliable. It is impossible to do this for each of the 100 or so lines in an image, to perform up to 400 flow calculations per line, and still achieve a frame rate which will produce a diagnostic moving image. This is a particular difficulty in infants and children in whom the heart rate may be very high. To achieve a compromise on the number of scan lines used for colour flow data, the width or sector angle of the

Requests for reprints to Mark J Monaghan, MSc, Cardiac Department, King's College Hospital, Denmark Hill, London SE5 9RS

colour image may be reduced to approximately 30° or 45° and flow data can be collected on alternate scan lines. Inevitably, this reduces the spatial resolution.

Ultra high-speed microprocessors have improved the processing speed of the flow calculations so that frame rates of, for example, 14 Hz at 16 cm over a 45° colour flow sector arc are now obtainable. Most conventional cross sectional images are displayed at 30 Hz over a 90° sector arc—more than double the colour flow frame rate. Again, some manufacturers have been more successful in achieving acceptable frame rates than others and this is an important factor in evaluating equipment. Low frame rates are distracting, causing flicker in a real time image so that important information may be missed.

Some manufacturers have incorporated a digital cine-loop image memory system into their instruments. This feature, which allows frame by frame replay and examination of high quality image data, is useful for analysing complicated or rapidly changing flow patterns or when copy of a precise flow event is required.

When conventional Doppler techniques are used, the presence of turbulent blood flow is inferred if there is "spectral broadening" in the flow signal. Since colour flow mapping is only capable of displaying the mean blood velocity at any point, turbulence may not be detected by the use of spectral broadening. An alternative method, that of "variance mapping", is therefore used.² For this technique, the spatial and temporal statistical variation in blood flow velocity and direction around every colour flow pixel is measured. If there is a high variance in the flow signals, then the blood flow at that point is assumed to be turbulent. The colour green is then added, at that point, to the other colours that would have been displayed. Variance or turbulence mapping is an option on most instruments and, when used, areas of turbulent flow are easily recognised by the presence of green. Theoretically, it is possible to quantify the amount of variance, and hence the turbulence, present in a flow jet. In the future this may have important applications including the serial monitoring of valve function.

As with conventional cross sectional imaging, artefacts in colour flow images may arise as a result of poor insonation between the transducer and the heart. In about 20% of adults interference by the lungs and ribs may cause a "noisy" colour display that detracts from the image quality and the diagnostic information. A distracting artefact that is specific to some colour flow instruments is widespread coloration of tissue areas of the image. These areas should only be displayed in grey scale because they do not contain moving blood. However, if these tissue areas (valves, myocardium) are themselves

moving, they may also generate a Doppler shift which the instrument then colour codes accordingly. This artefact has been reduced in some instruments by the use of a subtraction processing algorithm that only displays colour data in non-tissue areas and also by a filtering system based upon a "moving target indicator principle".

Since colour flow mapping is essentially a pulsed Doppler system, it too is limited by the maximum flow velocity that can be detected without aliasing. In fact, the velocity at which aliasing occurs is usually considerably lower with colour flow mapping than with conventional pulsed Doppler. Aliasing causes the ambiguous display of multiple colours in the flow jet. This is often described as a mosaic appearance. In theory, the fact that aliasing occurs at relatively low blood velocities (in relation to the transducer) is a disadvantage. In practice, this phenomenon is quite useful. Aliasing is very easy to identify. The mosaic appearance draws the eye to areas of higher and possibly turbulent blood flow so that abnormalities are usually easy to detect. Figures 2 and 4 give examples of aliasing.

It is important that the instrument displays the velocity and direction of blood flow in relation to the transducer. For example, an aortic regurgitant jet may be moving slightly away from the transducer when viewed in the parasternal long axis view. It will therefore be coloured blue with some aliasing through to red, depending on the relative velocity (fig 2). If the same jet is viewed from an apical position it will now be moving towards the transducer with a

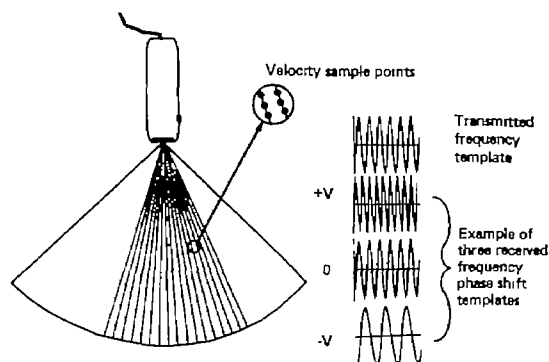


Fig 1 Autocorrelation method for flow estimation. Several points down selected scan lines are sampled and the received frequency waveform or phase shift is compared against a template of the transmitted frequency for each sample point. Frequency or phase shift templates for approximately 16 ranges of velocity and direction are stored within the instrument and the received data are matched to these templates to obtain an estimate of the mean flow velocity/direction. The mean flow velocity estimate is improved by increasing the number of times each scan line is sampled.



Fig 2 Diastolic parasternal long axis colour flow image showing aortic regurgitation (AR). In this plane the regurgitant jet was directed inferiorly away from the transducer and was therefore mainly coded as blue. Because the relative flow velocity was high and the jet was turbulent there was some aliasing through to red and yellow. The jet was broad and extended past the mitral valve to the posterior left ventricular wall. This was graded as moderate aortic regurgitation. AO, aorta; LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract.



Fig 3 Parasternal short axis image of flow through a small muscular ventricular septal defect (in the anterior septum) (IVS) into the right ventricle. The defect could not be visualised on cross sectional imaging without colour flow guidance, and the flow could not be readily detected by conventional Doppler. LVPW, left ventricular posterior wall. See legend to fig 2 for other abbreviations.

higher relative velocity. In this case the jet will be coloured red; however, there is likely to be multiple aliasing through to blue so that the flow jet will have a mosaic appearance. If a variance map is selected, then green will also be seen within the regurgitant jet (in either view) indicating that it is turbulent. This dependence on the relation between the direction of the flow jet and the transducer may be confusing at first. Future systems will evaluate the jet direction and display the flow colours that are dependent upon the true and not the relative blood velocity.

Applications

As with all Doppler techniques, colour flow mapping requires a good understanding of, and ability to perform, conventional ultrasound imaging. No real additional skill is required to obtain satisfactory colour flow images and the standard cross sectional imaging planes are used. The technique is at present qualitative rather than quantitative and it is unnecessary to "line up" with the flow as with conventional Doppler. Ease of use has been described as one of the advantages of this technique,³ though many manufacturers have made their colour flow instruments unnecessarily complicated and difficult to use. This may make this advantage difficult to realise. While there are many possible options for processing and display of colour flow data, in practice only a few of these are used and in many cases the instrument controls could be simplified. It would be more satisfactory for instruments to concentrate on those options that are known to be clinically useful.

The first commercial colour flow instruments were less sensitive than conventional Doppler technology. However, current instruments are just as sensitive. Continuous wave Doppler, with a dedicated Doppler transducer rather than an imaging transducer, remains the most sensitive technique. In practice, because colour flow mapping surveys the field of view, small elusive jets are comparatively easy to detect. These small jets may be missed by continuous or pulsed wave Doppler without detailed and time consuming searching.

In patients with multiple ventricular septal defects one or more of these may be missed by conventional Doppler. Because the eccentric jets of small ventricular septal defects are almost always of high velocity and turbulent, they are usually easy to find within the colour flow scan plane because they cause aliasing (mosaic pattern) and variance (green colour).⁴ Conventional continuous wave examination to record the jet velocity may then be performed, guided by the colour flow map. Figure 3 shows flow through a small muscular ventricular septal defect.

The situation may be similar in patients with prosthetic valves, where regurgitant jets (valvar or

paravalvar) are often very eccentric and difficult to display by conventional Doppler ultrasonography. Confusing colour flow artefacts may arise from the opening and closing of the prosthesis and, in addition, shadowing by the prosthetic valve may make it difficult to detect regurgitant jets in some imaging planes. There are, however, encouraging reports suggesting that assessment of prosthetic valves is quicker and more accurate by colour flow mapping than by conventional pulsed Doppler.⁵

Regurgitant lesions in native valves are easy to detect with colour flow mapping, and several studies have reported a high sensitivity and specificity.^{6,7} Measurement of severity, with angiography as the reference standard, has, however, been less successful.⁸ Superficially, angiography and colour flow mapping seem to provide similar types of flow images. The source data are, however, very different. With angiography, the severity of regurgitation is usually graded qualitatively by assessing the extent of opacification and clearance time of the contrast medium from the receiving chamber. Colour flow mapping on the other hand shows the spatial extent of the regurgitant jet velocities. Since the two techniques are measuring different variables, often under different physiological conditions, it is not surprising that the correlation is disappointing. Several measurement techniques for colour flow have been proposed including planimetry of the area of the regurgitant jet, measurement of its length, and also the width near its origin.^{9,10} Unfortunately, all these variables are influenced by several factors including the sensitivity of the instrument, gain settings, view used, the driving pressure of the regurgitant jet, and the precise part of the cardiac cycle in which the measurements are made. Despite these problems, the technique is more sensitive than auscultation (not always an advantage), much easier to perform than angiography, and can usually grade regurgitant lesions into the clinically relevant categories of mild, moderate, or severe.

One of the major limitations of conventional Doppler is that it does not enable the spatial orientation of blood flow jets to be seen as colour flow mapping does. For example, in cases of combined mitral stenosis and aortic regurgitation it can be difficult to separate the two diastolic flow jets in the left ventricle by conventional Doppler ultrasonography. Also, in patients with prosthetic valves and after balloon dilatation of stenotic native valves the flow patterns may be very complex and will often consist of multiple jets that could not be discerned or evaluated by pulsed Doppler. Patients with congenital cardiac lesions may also have complex multiple intracardiac shunts. Figure 4 shows severe mitral regurgitation. The spatial extent of this regurgitant jet would have been very difficult to evaluate by

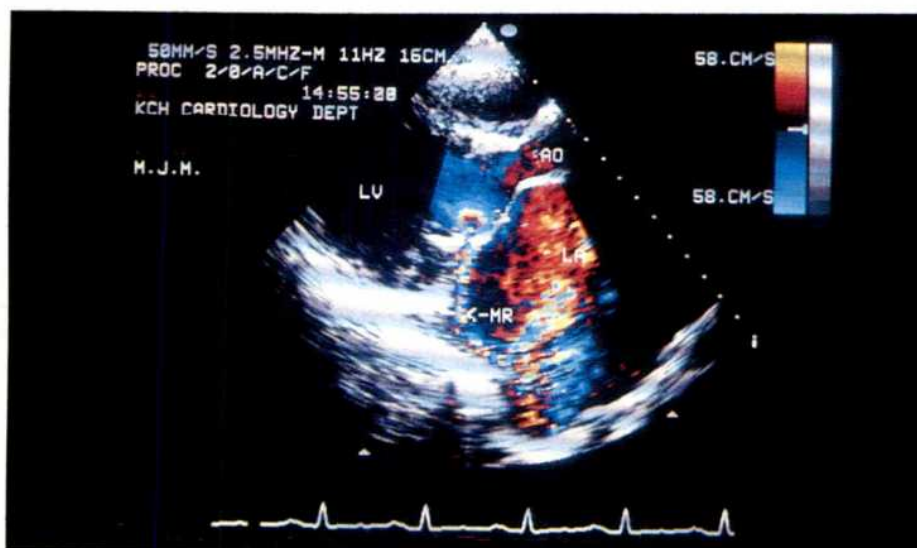


Fig 4 Parasternal long axis systolic frame of severe mitral regurgitation (MR) secondary to rheumatic valve disease. The anterior mitral valve leaflet was prolapsing behind the immobile posterior leaflet. The jet was therefore directed posteriorly along the wall of the left atrium and bounced back anteriorly (off the posterior left atrial wall anterior to the descending aorta). In the short axis plane, this same jet fanned out along the left atrial wall both medially and laterally and was approximately 3 cm wide. The close proximity of this jet to the atrial wall and its complex shape would have been difficult to identify by conventional pulsed Doppler. Acceleration of blood within the left ventricular cavity (proximal to the regurgitant orifice) was indicated by aliasing of the colour through to yellow and red. The jet velocity within the left atrium was considerably higher and therefore caused multiple aliasing, with a mosaic of colours, as it travelled posteriorly. When the jet bounced anteriorly it had spread out, lost energy and velocity, and so aliasing was not as prominent. The jet was therefore coded mainly yellow and red as it moved back towards the transducer. See legend to fig 2 for abbreviations.

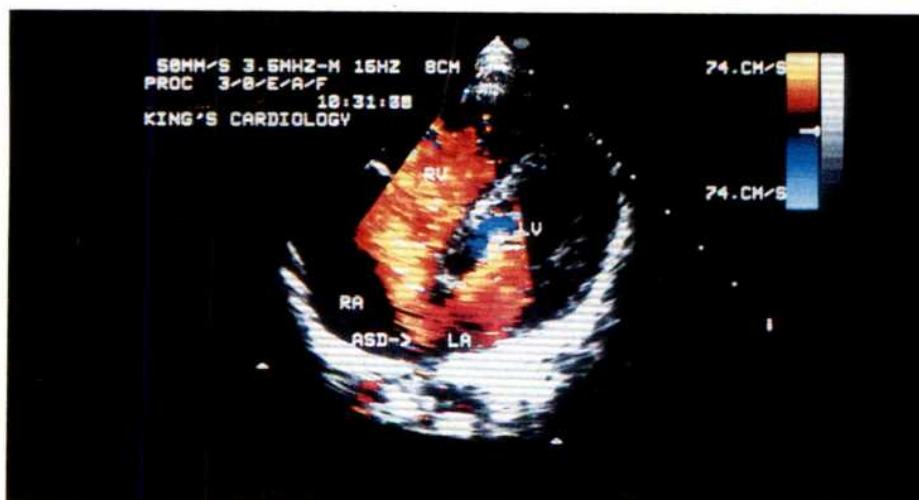


Fig 5 Considerable left to right shunting through a secundum atrial septal defect (ASD) seen in a modified apical four chamber view. As blood entered the left atrium from the superior pulmonary veins, traversed the atrial septum (and mitral valve), and crossed the tricuspid valve from the right atrium, it was moving towards the transducer and therefore was coloured red and yellow. The size of the shunt was assessed by examining the size of the flow jet within the right heart. The demonstration of transatrial shunting was so convincing that invasive investigations were not necessary before operation. In addition, it was possible to calculate the pulmonary artery systolic pressure from a tricuspid regurgitant jet and this confirmed the absence of important pulmonary hypertension. See legend to fig 2 for abbreviations.

conventional pulsed Doppler. Colour flow mapping may also assist and simplify quantitative measurements of flow velocity made with conventional Doppler. For example, it is very easy to identify the point of highest flow velocity on the colour flow map and then position the pulsed Doppler sample volume accordingly³ without making a search for the highest velocity point by repeatedly moving the pulsed Doppler sample volume in what amounts to a blind mapping procedure.

The spatial direction of a flow jet is almost impossible to predict accurately by imaging and conventional Doppler. However, if reliable quantitative measurements are to be made the jet direction must be known so that the Doppler beam can be oriented appropriately. There are many instances in which colour flow mapping may help to reduce the angle of incidence between the jet and the Doppler beam and therefore improve the accuracy of velocity and derived haemodynamic data. Examples include aortic stenosis, mitral stenosis, prosthetic mitral valves, ventricular septal defects, and tricuspid regurgitation. In tricuspid regurgitation the prediction of pulmonary artery systolic pressure can be improved if the continuous wave Doppler beam is aligned, with colour flow guidance along the direction of the tricuspid regurgitation.¹¹ Some instruments, which have the facility to perform continuous wave Doppler and colour flow mapping using the same transducer, allow for the angle to be corrected.⁴ It must be remembered, however, that flow jets are three dimensional and correction is possible in one plane only. Therefore, it is better practice to minimise any angle of incidence by adjusting the position of the transducer and checking the jet direction in two orthogonal imaging planes.

Despite the advantages of colour flow Doppler, some experienced echocardiographers still feel that it provides them with little additional information over and above conventional Doppler. On the other hand, many of those who now perform routine Doppler examinations have restricted experience and find colour flow mapping easier to perform and understand. Cardiologists or surgeons who are unfamiliar with conventional Doppler spectral recordings find colour flow images easier to assess and so their use may reduce the need for invasive investigation of flow abnormalities before operation. Figure 5 shows a secundum atrial septal defect in which considerable left to right shunting was clearly seen and for which further investigations before surgical closure were deemed unnecessary.

Most centres that have experience of colour flow mapping agree that the technique is especially useful for rapid screening to establish normal flow and that

it reduces the time spent on echocardiographic investigation.³ During the learning phase with colour Doppler we were able to increase the echocardiographic workload by 60% without an increase in staff. In busy departments, this advantage alone goes a long way towards justifying the use of the technique.

Transoesophageal echocardiography is a newer technique that is attracting much attention. When it is performed on conscious patients it is important to keep the examination time as short as possible. For this reason, colour flow mapping is now considered an essential adjunct to transoesophageal echocardiography.³

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Plasma atrial natriuretic peptide in patients with acute myocardial infarction: effects of streptokinase

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SUMMARY Plasma concentrations of immunoreactive atrial natriuretic peptide (mean (SEM)) were measured in 135 patients admitted to two coronary care units with myocardial infarction, ischaemic chest pain, or non-ischaemic chest pain. Concentrations were significantly higher in patients with acute myocardial infarction not treated with systemic thrombolysis (60.4 (14.3) pg/ml) than in patients with non-ischaemic chest pain (21.1 (4.3) pg/ml). Patients with ischaemic chest pain had intermediate values (39.3 (7.1) pg/ml). Patients with acute myocardial infarction treated with intravenous streptokinase had normal concentrations of plasma atrial natriuretic peptide (20.2 (3.6) pg/ml), which were significantly lower than those in patients with myocardial infarction not given streptokinase. These changes could not be explained by factors such as age, pre-existing hypertension, renal dysfunction, or cardiac failure, nor treatment other than streptokinase. Raised plasma concentrations of atrial natriuretic peptide in acute myocardial infarction may be a homeostatic response acting to reduce atrial pressures by natriuresis, diuresis, and venodilatation.

The lower concentrations of atrial natriuretic peptide in patients with acute myocardial infarction treated with streptokinase may reflect a short term beneficial haemodynamic effect of streptokinase.

Plasma concentrations of atrial natriuretic peptide are increased by plasma volume expansion¹⁻³ and are higher than normal in patients with congestive cardiac failure.⁴⁻¹⁰ This increase is probably a response to atrial distension and is probably a homeostatic mechanism to lower atrial pressures through natriuresis, diuresis, and venodilatation.^{4,11} Most studies of plasma atrial natriuretic peptide concentrations in human ventricular dysfunction have been performed in patients with chronic heart disease and overt fluid retention. We measured plasma concentrations of atrial natriuretic peptide in patients without a past history of cardiac failure when infarction was essentially complete but before appreciable volume expansion could occur. We wanted to find out whether plasma concentrations of atrial natriuretic peptide rise in response to acute left ventricular muscle dysfunction without volume expansion. We also aimed to assess the effect on

plasma concentrations of atrial natriuretic peptide of myocardial salvage by intravenous streptokinase.

Patients and methods

Blood samples were obtained from 196 consecutive fasting patients with chest pain admitted to the coronary care units of two university teaching hospitals. Blood was drawn at 0730 on the morning after admission before the patient got up. Patients with significantly impaired renal function (assessed by plasma concentrations of creatinine > 150 µmol/l) or with a past history of cardiac failure were excluded (26 patients) because plasma atrial natriuretic peptide is known to be raised in these conditions.^{4-10 12-15} Drug treatment, including intravenous streptokinase for evolving transmural myocardial infarction (1.5 million units within four hours of the onset of chest pain) was given as required. Patients were classified as having an acute myocardial infarction if they had all of: a compatible history, appropriate electrocardiographic changes, and peak plasma concentrations of creatine kinase or creatine kinase MB isoenzyme

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greater than or equal to twice the upper limit of normal (upper limits of normal: creatine kinase 160 IU/l (2.66 μ kat/l) creatine kinase MB isoenzyme 22 IU/l (0.22 μ kat/l)). The infarct site was classified as anterior or inferior. Patients were considered to have ischaemic chest pain if they had anginal pain but no enzyme rise or subsequent permanent electrocardiographic changes. Patients were classified as having non-ischaemic chest pain if an alternative diagnosis was established or if after subsequent extensive investigation (for example coronary angiography) no evidence for acute myocardial ischaemia could be found. Thirty five patients who did not fulfil these classification criteria were excluded. Cardiac failure was graded as Killip class I-IV.¹⁶ The approval of the ethics committee was obtained before the study.

RADIOIMMUNOASSAY FOR ATRIAL NATRIURETIC PEPTIDE

Blood (10 ml) was taken into chilled tubes containing edetic acid (0.15 nmol) and 500 kallikrein inhibitor units of aprotinin (Trasylol, Bayer), placed on ice, centrifuged at 4°C, and the plasma was stored at -20°C until radioimmunoassay.¹⁴ The inter-assay and intra-assay coefficients of variation are 12.4% and 6.4% respectively. The normal range is 10-40 pg/ml with a lower limit of detection of 4 pg/ml.¹⁴

STATISTICAL ANALYSIS

Plasma concentrations of atrial natriuretic peptide were log transformed because the results were not normally distributed. We used analyses of variance and covariance, correlations, and unpaired *t* tests on continuous variables, and χ^2 tests on categorical variables. If a significant main effect was found by analysis of variance we measured individual differences between means by the Newman-Keuls retrospective comparisons test. Data for continuous variables are presented as means (SEM).

Results

The table shows details of the patients. The distribution of sex, systolic and diastolic blood pressure, pulse rate, or past history of hypertension was similar in all the groups. The plasma concentration of creatinine was significantly higher in patients with acute myocardial infarction treated with streptokinase than in patients with non-ischaemic chest pain ($p < 0.01$). Past myocardial infarction was more common in those with ischaemic chest pain ($p < 0.001$).

Plasma concentrations of atrial natriuretic peptide were significantly higher ($p < 0.01$) in those with acute myocardial infarction not treated with strep-

Table Clinical details (mean (SEM) or %) of the patients studied

	NICP	ICP	AMI no SK	AMI SK
No of patients	18	52	43	22
Women (%)	8 (44)	24 (46)	10 (23)	5 (23)
Men (%)	10 (56)	28 (54)	33 (77)	17 (77)
Age (years)	52 (2)	62 (1)	61 (2)	54 (2)
Plasma creatinine (μ mol/l)	81 (3)	88 (2)	91 (3)	97 (4)
Systolic blood pressure (mm Hg)	126 (2)	125 (2)	121 (2)	121 (4)
Diastolic blood pressure (mm Hg)	75 (2)	73 (2)	72 (2)	76 (3)
Pulse rate (beats/min)	72 (2)	73 (3)	74 (2)	82 (3)
No with past hypertension (%)	11 (61)	27 (52)	17 (40)	11 (50)
No with past myocardial infarction (%)	3 (17)	34 (65)	6 (14)	4 (18)
No in Killip class I (%)	17 (94)	46 (89)	29 (67)	18 (82)
No in Killip class > I (%)	1 (6)	6 (11)	14 (33)	4 (18)

AMI, acute myocardial infarction; ICP, ischaemic chest pain; NICP, non-ischaemic chest pain, SK, streptokinase.

tokinase (60.4 (14.3) pg/ml) than in those with non-ischaemic chest pain (21.1 (4.3) pg/ml) but not different from those in patients with ischaemic chest pain (39.3 (7.1) pg/ml). The most striking finding, however, was the normal plasma concentration of atrial natriuretic peptide in patients with acute myocardial infarction treated with streptokinase (20.1 (3.6) pg/ml). This was significantly lower ($p < 0.01$) than that in patients with acute myocardial infarction not treated with streptokinase. These differences were not explained by the lower age^{17,18} of the patients with acute myocardial infarction treated with streptokinase and those with non-ischaemic chest pain compared with the other two groups ($p < 0.05$), because analysis of covariance of the data on plasma concentrations of atrial natriuretic peptide with age as covariate showed the same differences ($p < 0.001$). Nor was this difference caused by differences in treatment (intravenous fluids, long acting nitrates, β blockers, calcium antagonists, angiotensin converting enzyme inhibitors, vasodilators, digoxin, inotropes, atropine) before blood sampling as usage of these drugs was similar in each group. Opiates were used more frequently in those with acute myocardial infarction treated with streptokinase, and less often in patients with ischaemic chest pain ($p < 0.001$). Opiates were usually administered before admission to the coronary care unit, 8-32 hours before blood sampling for estimation of plasma concentrations of atrial natriuretic peptide. Treatment with diuretics (mostly as part of a regular regimen for hypertension) was more common in patients with ischaemic chest pain ($p < 0.05$).

There was an excess of patients with signs of cardiac failure (Killip class > 1) in patients with acute myocardial infarction not treated with streptokinase ($p < 0.05$). Overall, plasma concentrations of atrial natriuretic peptide were higher ($p < 0.01$) in patients in Killip class II (65.7 (15.7) pg/ml , $n = 24$) than in those in Killip class I (33.9 (5.6) pg/ml , $n = 110$). There was only one patient in Killip class III and his plasma concentration of atrial natriuretic peptide was 158.8 pg/ml . Patients with existing cardiac failure were excluded at the start of the trial.

There was a significant correlation between plasma atrial natriuretic peptide and age ($r = 0.37$, $p < 0.001$) but no significant correlation with plasma creatinine, probably because patients with significantly impaired renal function had been excluded. There was no significant correlation between plasma atrial natriuretic peptide and peak concentrations of cardiac enzymes.

Although plasma concentrations of atrial natriuretic peptide were slightly higher in patients with inferior infarcts (56.2 (17.3) pg/ml , $n = 34$) than in those with anterior infarcts (36.4 (8.0) pg/ml , $n = 31$) this difference was not statistically significant. Similarly, there was no difference in plasma concentrations of atrial natriuretic peptide between transmural and non-transmural acute myocardial infarction.

Discussion

Atrial distension is probably the main stimulus to secretion of atrial natriuretic peptide.^{3,6-9,19,20} In patients with chronic congestive cardiac failure ventricular dysfunction and fluid retention coexist and lead to increased atrial pressures and raised plasma concentrations of atrial natriuretic peptide.⁴⁻¹⁰ In rats with experimental infarction plasma concentrations of atrial natriuretic peptide are raised in proportion to myocardial dysfunction and infarct size²¹ without expansion of extracellular fluid volume.²² Similarly, we found raised plasma concentrations of atrial natriuretic peptide in patients during the acute stage of myocardial infarction before appreciable fluid retention could occur and lead to an additional increase in atrial pressures. Thus these results suggest that acute myocardial dysfunction alone, by reducing diastolic ventricular compliance and raising atrial pressures, may increase plasma concentrations of atrial natriuretic peptide. Plasma concentrations of atrial natriuretic peptide were also higher in patients in whom signs of cardiac failure developed. This result accorded with previous findings.⁴⁻¹⁰ Since atrial natriuretic peptide causes venodilatation, natriuresis, and diuresis,^{4,11} raised concentrations of atrial natriuretic peptide may be beneficial in acute

myocardial infarction because they will reduce cardiac preload²³ and salt and water retention and so limit pulmonary oedema.

Plasma concentrations of atrial natriuretic peptide were reported in a study of patients with acute myocardial infarction.²⁴ In that study, however, the control group was not under the same conditions of coronary care as the patients with infarcts nor were the concentrations of atrial natriuretic peptide corrected for the younger age of the controls; this may have confounded the findings of higher plasma concentrations of atrial natriuretic peptide in acute myocardial infarction.²⁴ None the less, our study confirms and extends these findings.

Of interest was the normal mean plasma concentration of atrial natriuretic peptide in patients with acute myocardial infarction treated with streptokinase, compared with the threefold higher concentration in acute myocardial infarction patients not treated by thrombolysis. One explanation for this would be the beneficial effect of intravenous streptokinase given within four hours of the onset of chest pain in acute myocardial infarction in preserving the myocardium and myocardial function.²⁵ Since plasma concentrations of atrial natriuretic peptide are raised in proportion to haemodynamic dysfunction⁵⁻⁹ one might expect lower plasma concentrations of atrial natriuretic peptide in patients with acute myocardial infarction treated successfully with streptokinase.

Other factors might also have a role. Streptokinase catalyses the conversion of plasminogen to the protease plasmin. It is unlikely that streptokinase led to degradation of the atrial natriuretic peptide and lower plasma concentrations of atrial natriuretic peptide because streptokinase added to the assay system for atrial natriuretic peptide assay did not affect concentrations of atrial natriuretic peptide (P A Phillips, G P Hodsman, C I Johnston, unpublished observation). Streptokinase is unlikely to have had a proteolytic effect at the time of sampling because (a) streptokinase has a fibrinolytic half life of approximately 15–30 min,²⁶ (b) blood samples for the measurement of plasma atrial natriuretic peptide were taken at least seven hours after streptokinase treatment, and (c) atrial natriuretic peptide has a plasma half life of 2–3 min.²⁷ Another factor that might have led to lower plasma concentrations of atrial natriuretic peptide after streptokinase might be the vasodilatory effects of fibrin and fibrinogen degradation products.²⁸

A further explanation for the lower concentrations of plasma atrial natriuretic peptide in patients with acute myocardial infarction treated with streptokinase might be differing drug treatment. This too seems unlikely since opiates were the only drugs given more

often to patients who received streptokinase, and these were usually given several hours before blood sampling. Furthermore, morphine raised plasma atrial natriuretic peptide in rats²⁹ and so would be unlikely to lead to the lower concentrations of atrial natriuretic peptide seen in this study. Similarly, the lower concentrations of atrial natriuretic peptide cannot be explained by the lower age^{18,19} of the patients treated with streptokinase, because analysis of covariance controlling for age showed that age was not a confounding factor. Nor does arrhythmia^{30,31} or raised blood pressure⁸ explain the differences in plasma concentrations of atrial natriuretic peptide across the groups because pulse rates and systolic and diastolic blood pressures were similar. The presence of other conditions that might influence plasma atrial natriuretic peptide (renal impairment,¹²⁻¹⁵ previous hypertension,^{8,9} previous myocardial infarction⁷) would also not explain the results. Patients with renal impairment were excluded, and those with the lowest plasma concentrations of atrial natriuretic peptide (those with acute myocardial infarction treated with streptokinase) had the highest plasma creatinine. Hypertension was equally prevalent across the groups and past myocardial infarction was more common in the group with ischaemic chest pain.

Patients with ischaemic chest pain had a mean plasma atrial natriuretic peptide concentration intermediate between that of patients with acute myocardial infarction and that of patients with non-ischaemic chest pain. This suggests that concentrations of atrial natriuretic peptide may rise in response to ventricular diastolic dysfunction secondary to myocardial ischaemia. Unfortunately because this group had a higher prevalence of previous myocardial infarction, which might raise plasma atrial natriuretic peptide,⁷ as well as diuretic therapy, which might lower plasma atrial natriuretic peptide,¹⁰ these results are difficult to interpret.

In summary, the results show that plasma concentrations of atrial natriuretic peptide are raised in the acute phase of myocardial infarction. This accords with the concept that myocardial dysfunction without volume overload can lead to raised atrial pressures and release of atrial natriuretic peptide. Because atrial natriuretic peptide causes natriuresis, diuresis, and venodilatation,^{4,11} raised concentrations of atrial natriuretic peptide might therefore be beneficial by reducing cardiac preload and limiting salt and water retention and pulmonary oedema during the acute stages of myocardial ischaemia. The mean plasma concentration of atrial natriuretic peptide was normal in patients with acute myocardial infarction treated with streptokinase. This may reflect improved haemodynamic function because of myocardial salvage with streptokinase. Further

studies are needed to see if the estimation of plasma atrial natriuretic peptide in the acute phase of acute myocardial infarction is a predictor of outcome, especially after streptokinase treatment, and whether atrial natriuretic peptide analogues are likely to be useful in the management of myocardial infarction.

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Relation of third and fourth heart sounds to blood velocity during left ventricular filling

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SUMMARY To investigate the relation between changes in left ventricular inflow velocity and the timing of third and fourth heart sounds, simultaneous phonocardiograms and continuous wave Doppler traces were recorded in 48 patients (aged 17-78) with heart disease and in 21 normal children. The onset of the first vibration of the third heart sound coincided with peak left ventricular inflow blood velocity to within 5 ms in all but two of the patients. The mean (SD) difference between the two events was 5 (5) ms, which did not differ significantly from zero. The relation was similar in patients with primary myocardial disease (11), and in those with valve disease (26), hypertension (five), and coronary artery disease (four). In the normal children, the mean interval was 2.5 (5) ms—not significantly different from zero. By contrast, the first deflection of the fourth heart sound consistently preceded the timing of peak atrial inflow velocity by 55 (10) ms. Agreement was much closer between the onset of atrial flow and the onset of the atrial sound (mean difference 1 (5) ms, not significantly different from zero). Gallop sounds seem to be closely related to changes in ventricular inflow velocity, and thus to the effects of forces acting on blood flow. The forces underlying the third sound seem to arise within the ventricle and are responsible for sudden deceleration of flow during rapid ventricular filling. The fourth sound, occurring at the onset of the “a” wave, is more likely to arise from dissipation of forces causing acceleration of blood flow—that is, atrial systole itself.

The third and fourth heart sounds, termed “gallop sounds” by Bouillaud in 1847¹ are widely recognised to be of great clinical importance as evidence of ventricular disease. Despite this long history their exact origin remains controversial though they are generally believed to be related in some way to ventricular filling. We compared the timing of the third and fourth heart sounds with that of ventricular filling velocities as shown by continuous wave Doppler echocardiography. In this way, we hoped to explore their relation to the timing of blood flow and thus to the forces governing its rate of change.

Patients and methods

We investigated 48 patients (29 men, 19 women) aged 17-78 years with clinical evidence of left ventricular disease or non-rheumatic mitral regurgitation. The table gives the underlying diagnoses and occurrence

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of added sounds. We also studied 21 children (15 boys, six girls) aged 4-13 years. A third or fourth heart sound was audible in all the individuals studied.

Examinations by continuous wave Doppler were performed with a 2 MHz 1 cm transducer positioned at the apex and directed towards the mitral valve. The direction of the ultrasound beam was always to the left and lateral to the characteristic velocities recorded in the left ventricular outflow tract during ejection and thus distinguished mitral from tricuspid flow. A Doptek spectral analyser was used, and the transducer was angled, with the aid of the audio

Table Causes of added sounds

Diagnosis	III alone	IV alone	III + IV
Hypertrophic cardiomyopathy (6)	1	3	2
Aortic stenosis (11)	9	1	1
Hypertensive heart disease (5)	1	2	2
Aortic regurgitation (7)	4	2	1
Mitral regurgitation (8)	5	0	3
Dilated cardiomyopathy (5)	4	1	0
Ischaemic heart disease (4)	1	1	2
Restrictive cardiomyopathy (2)	1	1	0

III, third heart sound, IV, fourth heart sound.

signal, to obtain maximum velocities of forward mitral flow, independent of mitral cusp artefacts. The delay imposed by spectral analysis was measured directly and found to be <5 ms. The standard lead II of the electrocardiogram and the phonocardiogram were both recorded simultaneously, the latter with a Leatham microphone from two positions: from the apex, with a low frequency filter, where the added sounds were most clearly audible; and from the left sternal edge, with a medium frequency filter, where splitting of the second sound was most obvious. Apexcardiograms were recorded with a Cambridge Instruments transducer with a time constant of 4 s from the apex, along with simultaneous phonocardiograms and the standard lead II of the electrocardiogram. All recordings were made with a photographic strip chart recorder at a paper speed of 100 mm/s.

The following time intervals were measured with callipers for each patient:

- The time interval between the peak flow velocity on the Doppler trace during early diastole and the onset of the first vibration of the third heart sound. This was either measured directly, or, in a minority when the third sound and the Doppler cardiogram could only be recorded from the same or overlapping positions on the thorax, as the difference between the intervals from the onset of the second heart sound to peak velocity of early filling and the first vibration of the third sound.
- The interval from the first vibration of the third sound to the "f" point of the rapid filling wave of the apexcardiogram.
- The interval between peak flow velocity during atrial systole to the onset of the first vibration of the fourth heart sound.
- The interval from the onset of the flow velocity increase at the start of atrial systole to the onset of the first vibration of the fourth heart sound.

All measurements were averaged over five successive beats and given to the nearest 5 ms. Data are expressed as mean (1 SD). The statistical significance of differences between mean values was investigated using Student's *t* test.

Results

THIRD HEART SOUND

The first vibration of the third sound corresponded to within 5 ms with the peak velocity recorded on the Doppler trace in all but two of the 37 patients (figs 1 and 2). In the whole group, the mean time interval between the peak velocity and third heart sound was 5 (5) ms. There was no significant difference between values in patients with mitral regurgitation (eight cases) and those with primary left ventricular

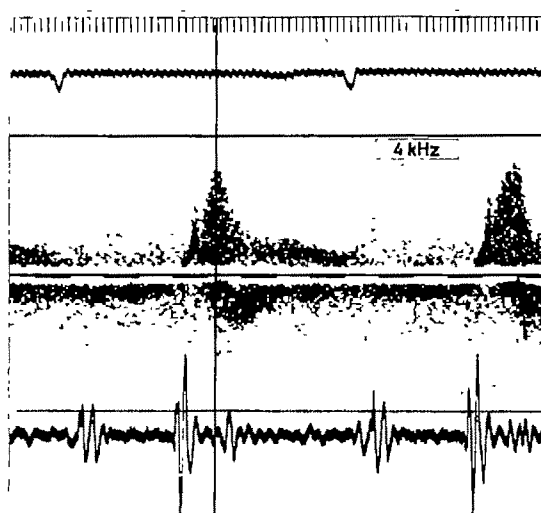


Fig 1 Simultaneous phonocardiogram, apical Doppler echocardiogram, and electrocardiogram from a patient with dilated cardiomyopathy showing a third heart sound. Vertical line represents timing of peak left ventricular inflow velocity on the Doppler recording which corresponds with the onset of the third sound.

disease (29 cases). In 16 of the normal children the onset of the third sound corresponded to within 5 ms of the peak velocity—preceding it in two, and in three following it by 10 ms. The mean difference between peak velocity was 2.5 (5) ms. Neither of these mean values was significantly different from zero.

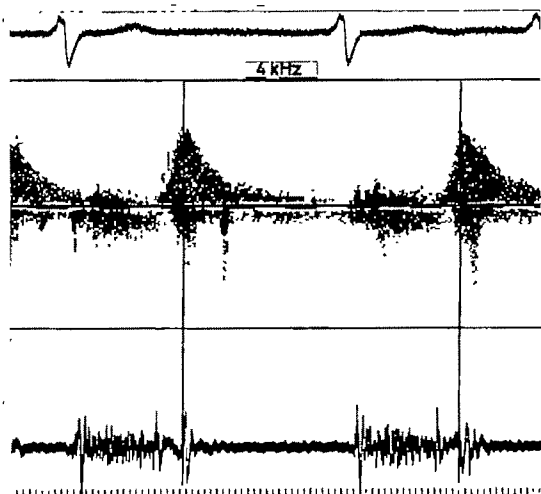


Fig 2 Simultaneous phonocardiogram, apical Doppler echocardiogram, and electrocardiogram from a patient with non-rheumatic mitral regurgitation. The vertical line shows the peak mitral flow velocity and corresponds with the initial vibration of the third heart sound.

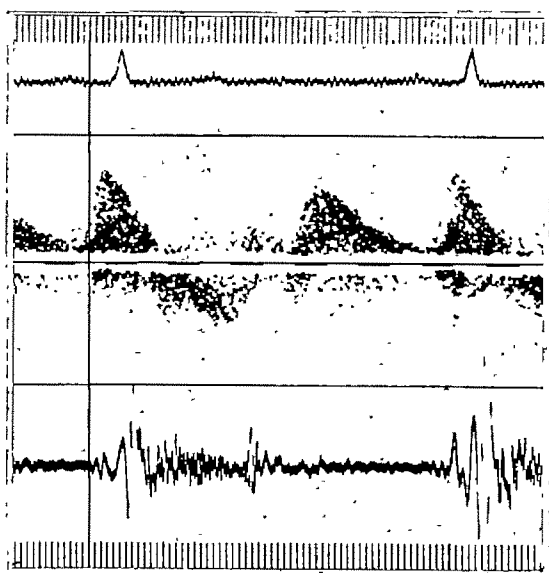


Fig 3 Simultaneous phonocardiogram, Doppler echocardiogram, and electrocardiogram from a patient with hypertensive heart disease and a fourth heart sound. Vertical line represents the onset of the fourth sound. This corresponds with the onset rather than the peak of the flow velocity trace during the "a" wave. (Doppler calibration: full scale deflection = ± 4 kHz.)

Satisfactory apexcardiograms were obtained in 33 patients and 16 of the normal children. The first vibration of the third heart sound consistently preceded the "f" point of the apexcardiogram both in the patients (mean 55 (10) ms) and in the normal children (mean 20 (5) ms), both values differing significantly from zero ($p < 0.01$ for both).

ATRIAL SOUND (FIGURE 3)

The first deflection of the fourth heart sound consistently occurred 55 (10) s before the time of the peak velocity of the "a" wave of the Doppler trace in all of the 22 patients in whom it was present. This value was significantly different from zero ($p < 0.001$). There was very much closer agreement between the onset of the atrial flow velocity curve and the onset of the first vibration of the fourth heart sound, the mean difference between the two events being only 1 (2.5) ms, a value that did not differ significantly from zero.

Discussion

Despite their clinical importance, there is still no consensus on the genesis of the third and fourth heart sounds. It seems to be generally agreed that they are related, at least indirectly, to ventricular filling, the

third heart sound to the rapid filling phase and the fourth to atrial systole. The original evidence for this came from Thayer in 1909. He showed a relation between the third sound and the "rapid filling wave" of the apexcardiogram.² Since then it has become apparent that events on the apexcardiogram are not closely related to volume changes in the left ventricle during diastole; in particular the "O" point is independent of mitral valve opening, and the peak rate of volume increase usually precedes the "rapid filling wave" although the third sound frequently coincides with the "f" point. Angiographic studies have shown that ventricular filling rates in patients with a third heart sound can be high or low.⁴ The third heart sound occurred 50 (40) ms after the peak rate of increase of the transverse dimension of the left ventricle measured by M mode echocardiography and there was a suggestion of a relation between a discontinuity on the dimension trace and the end of rapid filling.³ More recently, though, experimental¹⁵ and limited clinical⁷ studies have both shown an association between the third sound and sudden reduction in the rate of increase of the long axis but not the minor axis 48 (21) ms after the corresponding event on the minor axis. This delay is thus very similar to the interval previously reported by Prewitt *et al*³ between the third sound and the peak rate of increase in minor axis. The mechanism underlying this sudden deceleration has not been established, though the persistence of a third heart sound after replacement of the mitral and tricuspid valves showed that the subvalve apparatus was not necessarily involved.^{8,9}

The timing of the third heart sound is also closely related to changes in atrial and ventricular pressure. During the early period of ventricular filling, ventricular pressure first falls, and then rises rapidly, causing the atrioventricular pressure gradient to reverse, leading to a deceleration of ventricular inflow. It is during this period of deceleration that the third sound occurs.^{10,11} Our results thus closely agree with these findings. The third heart sound occurred at the time of peak velocity of inflow, marking the time at which acceleration had ceased. Acceleration of fluid is associated with a pressure gradient in the same direction as flow, and deceleration with a gradient in the reverse direction. Our finding that the third sound occurred when acceleration had ceased is thus equivalent to the results of van-de-Werf *et al* who showed that it followed reversal of the pressure gradient.^{10,11} The sudden change from acceleration to deceleration requires the operation of a force and the dissipation of energy; it is thus likely that this energy appears, in part, as the mechanical vibrations which form the third heart sound.

Like the third heart sound, the fourth sound is

associated with a period of increased rate of ventricular inflow. Its audibility is evidence of ventricular disease,^{12,13} although a low frequency event can sometimes be recorded phonocardiographically in normal subjects during atrial systole.¹⁴ As in early diastole, its timing has been related to reversal of the atrioventricular pressure gradient with atrial systole.^{10,11} Unlike the third sound, however, we found that the onset of the fourth heart sound corresponded with the onset rather than with the peak of the flow velocity trace. The force generating the fourth heart sound, therefore, seems to be the one that accelerates the blood into the ventricle, and so is the result of left atrial systole rather than some ventricular factor impeding blood flow as occurs with the third sound.

Doppler estimates of blood flow velocity are subject to certain technical limitations. They are confined to the region examined by the ultrasound beam, and so may not necessarily be representative of the entire ventricular inflow. However, the change in velocity with time is so abrupt that it seems unlikely that there could be wide differences within the column of blood moving into the ventricle without pronounced velocity gradients developing, and there is no experimental evidence of this. The use of continuous wave rather than pulsed Doppler echocardiography has the advantage that the maximum blood velocity is measured, regardless of its distance from the transducer; there seemed no particular reason to believe that the timing of added sounds would be related to blood velocities at specific positions within the ventricle such as the region just below the mitral cusps. The patients had clear evidence of left sided disease, so their third heart sounds probably arose from the left ventricle. A right sided third heart sound would not necessarily be expected to bear any consistent relation to the timing of left sided filling. An example is given in fig 4, from a patient with right ventricular disease, where the timing of the third sound was closely related to inflow velocities in the superior vena cava; peak mitral flow occurred 50 ms later.

The characteristic relation between ventricular filling velocities and the timing of added sounds provides information about the genesis of these sounds, but does not explain why they are audible in some patients and not in others. Presumably, ventricular diastolic properties must also be taken into account in predicting the nature of the forces that modify blood flow, in determining their timing, and in governing the extent to which the resulting energy dissipation will be converted to longitudinal vibrations audible as sound. For the fourth heart sound, atrial systolic function as well as ventricular diastolic properties must also be considered. Nevertheless, our results extend traditional lines of thought about

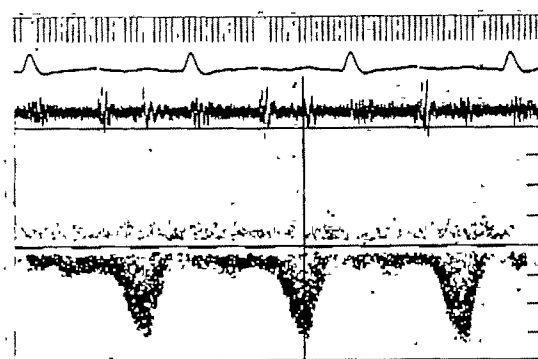


Fig 4 Simultaneous phonocardiogram, electrocardiogram, and Doppler echocardiogram from a patient with right ventricular disease caused by anterior mediastinal radiotherapy. The diagnosis of restriction was confirmed at thoracotomy. The Doppler echocardiogram is recorded from the suprasternal notch and shows the flow velocity in the superior vena cava. The vertical line shows the peak blood velocity which corresponds with the onset of a third heart sound. (Doppler calibration: full scale deflection = ± 8 kHz.)

the genesis of these abnormal sounds. They confirm their close relation to the processes underlying ventricular filling.¹⁵

Our results indicate that the physiological third sound has a similar time relation to ventricular inflow velocities and their rate of change as that associated with mitral regurgitation or ventricular disease. We did not confirm the recent suggestion that the third sound is caused by the ventricle impinging on the thoracic cage.¹⁶ Our observations raise the possibility that the Doppler trace may be a useful reference for analysing these events, particularly when their underlying mechanism is not clear—in some cases, for example, a summation gallop may result primarily from atrial systole, when the onset of the sound coincides with that of the increase in flow velocity, while in others it has the characteristics of a third sound even though it occurs after the P wave of the succeeding beat.

Finally, our results allow a unitary concept to be developed to explain the genesis of these added sounds—that is, they are the result of the dissipation of energy generated by the forces that cause changes in blood flow velocity. If this is proved, it gives a basis whereby these sounds, whose clinical importance has been so long and widely recognised, can be related more closely to the fundamental processes of ventricular filling, and thus to overall diastolic function in health and disease.

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Impaired blood pressure response to exercise in patients with coronary artery disease: possible contribution of attenuated reflex vasoconstriction in non-exercising muscles

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SUMMARY Eighteen patients with coronary artery disease were divided into two groups according to whether their blood pressure decreased (eight, group 1) or increased (10, group 2) in response to treadmill exercise testing. Age and the extent and distribution of coronary artery disease were similar in the two groups. At rest, blood pressure, pulmonary artery wedge pressure, cardiac index, forearm vascular resistance, and oxygen consumption were similar in the two groups. During supine leg exercise on a bicycle ergometer mean blood pressure increased in group 2 but did not change in group 1. Increases in cardiac index, pulmonary artery wedge pressure, and oxygen consumption during leg exercise were not significantly different in the two groups but forearm vascular resistance increased less in group 1 than in group 2. There was a positive correlation between the magnitude of the change in mean blood pressure and change in forearm vascular resistance during leg exercise. The impaired response of blood pressure to leg exercise in group 1 was not the result of a failure of the cardiac index to increase.

The results suggest the possibility that attenuation of reflex vasoconstriction in non-exercising muscles may contribute to the impaired response of blood pressure to exercise in patients with coronary artery disease.

In some patients with severe coronary artery disease the response of blood pressure to exercise is impaired.¹⁻³ The mechanisms for this are not known, although many believe that acute, ischaemia induced pump failure is responsible.^{1,4} But we know of no study that shows a decrease in cardiac output or the development of acute pump failure during exercise in patients with severe coronary artery disease.

A report that hypotension did not develop with pacing induced angina in patients who had exertional hypotension accompanying angina¹ raises the possibility that the response of blood pressure to exercise is impaired by altered control of vascular resistance during exercise rather than myocardial ischaemia itself. It has been suggested that exertional hypoten-

sion in patients with severe aortic stenosis may in part be the result of failure to produce reflex vasoconstriction in non-exercising muscles during exercise.⁵

We examined haemodynamic and forearm vascular responses to supine leg exercise with a cycle ergometer in patients with coronary artery disease who had a normal hypertensive response and in those in whom this response was impaired.

Patients and methods

We studied 18 patients with coronary artery disease (17 men and a woman, aged 39-72). Fourteen had a history of angina pectoris and 15 had had a myocardial infarction. In every patient coronary cine-angiography showed coronary artery stenosis that reduced the luminal diameter by >75%. No patient had a history of congestive heart failure or syncope during exercise. Valve disease was excluded by cross sectional and Doppler echocardiograms in every patient.

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TREADMILL EXERCISE TESTING

The patients were tested on a treadmill by the Bruce protocol.⁶ During treadmill exercise testing the electrocardiogram was monitored and blood pressure was measured by a sphygmomanometer every minute and at the end of exercise. Exercise testing was stopped by chest pain in eight patients, dyspnoea in eight patients, horizontal ST depression ≥ 0.2 mV in one patient, and the decrease in systolic blood pressure ≥ 10 mm Hg in another.

The patients were divided into two groups according to whether their mean blood pressure decreased (group 1, $n = 8$) or increased (group 2, $n = 10$) in response to treadmill exercise testing. Mean blood pressure in group 1 fell by 3–15 mm Hg (mean (SE) 8 (2) mm Hg) and increased in group 2 by 7–32 mm Hg (mean (SE) 18 (3) mm Hg). We calculated mean blood pressure by adding one third of the pulse pressure to the diastolic blood pressure. We used the blood pressure value measured immediately before the end of exercise testing for classification. In 12 patients exercise testing was done while they were off all medication. Six patients (three in each group) underwent exercise testing while they were on anti-anginal drugs, which included isosorbide dinitrate in combination with diltiazem, nifedipine, or nicorandil. During exercise no patient fainted or had arrhythmias such as ventricular tachycardia or atrioventricular block.

CARDIAC CATHETERISATION

All antianginal drugs were stopped 24 hours before cardiac catheterisation, and minor tranquillisers (diazepam 5 mg and pentobarbital 50 mg) were given orally 30 minutes before catheterisation. Pressures in the cardiac chambers and the aorta were measured by transducers (Bentley Tantec model 800). Cardiac output was measured by the thermodilution method and a thermocomputer (9520A Cardiac Output Computer, American Edwards Laboratories). Selective coronary angiography was performed in multiple projections by the Sones technique. Significant coronary stenosis was defined as a $\geq 75\%$ reduction in the internal diameter. Biplane left ventriculography was performed in the 30° right anterior oblique and 60° left anterior oblique projections. The left ventricular volume was measured by the Dodge biplane method.⁷ The ejection fraction was calculated as follows: left ventricular stroke volume $\times$ 100/left ventricular end diastolic volume.

ERGOMETER EXERCISE TESTING

After diagnostic cardiac catheterisation the patients performed leg exercise with a bicycle ergometer in a supine position at a workload of 20 W for six minutes. This low workload was chosen so that all

patients would be able to exercise for at least six minutes for a complete set of measurements. At least 20 minutes were allowed for patients to recover from diagnostic catheterisation. Aortic and pulmonary artery wedge pressures were recorded and cardiac output was measured by the thermodilution method before and during the last three minutes of exercise testing. The oxygen saturation of blood taken from the aorta and pulmonary artery was measured before and during the last minute of exercise testing. Oxygen consumption was calculated by multiplying the arteriovenous oxygen difference by the cardiac output. All patients completed six minutes of exercise testing without developing angina or severe dyspnoea.

MEASUREMENTS OF FOREARM BLOOD FLOW

Blood flow in the forearm was measured throughout ergometer exercise testing by a mercury in silastic strain gauge plethysmograph and the venous occlusion technique.⁸ A strain gauge plethysmograph was placed around the left forearm approximately 5 cm below the antecubital crease. The pressure in the cuff was 40 mm Hg.⁹ Circulation to the hand was stopped by inflating a cuff around the wrist to suprasystolic pressures when blood flow in the forearm was measured. We took the average of four to eight flow measurements made at 15 second intervals. Forearm vascular resistance was calculated by dividing mean aortic pressure (mm Hg) by forearm blood flow (ml/min/100 ml of forearm volume). These values are expressed as resistance units throughout this report. Forearm vascular resistances before exercise and during the last two minutes of exercise testing were compared.

Table 1 Baseline characteristics (mean (SEM)) of patients

	Group 1	Group 2	<i>p</i> value* (group 1 vs group 2)
Number	8	10	—
Age (yr)	58 (3)	53 (3)	NS
OMI†			
Total	6	9	—
Anteroseptal	3	4	—
Inferior	3	5	—
History of angina	7	7	—
CAD IVD/2VD/3VD	5/2/1	6/4/0	—
RCA/LAD/LCX	5/6/1	5/6/3	—
LVEF (%)	59 (6)	56 (4)	NS
LVEDP (mm Hg)	13(3)	16(3)	NS

**t* Test.

OMI, old myocardial infarction; CAD, coronary artery disease, VD, vessel disease, RCA, LAD, LCX—right, left anterior descending, and left circumflex artery respectively, LVEF, left ventricular ejection fraction, LVEDP, left ventricular end diastolic pressure.

Table 2 Heart rate and blood pressure responses to standing and treadmill exercise and the duration of exercise

			Group 1 (n = 8)	Group 2 (n = 10)	p value (Group 1 vs Group 2)
BP (mm Hg)	Systolic:	Rest	133 (8)	120 (5)	NS
		Standing	132 (6)	121 (6)	NS
		End of exercise	132 (7)	163 (8)***	<0.02
	Diastolic:	Rest	80 (5)	76 (5)	NS
		Standing	85 (4)*	82 (5)*	NS
		End of exercise	73 (4)***	88 (5)	<0.05
	Mean:	Rest	98 (6)	91 (5)	NS
		Standing	100 (5)	95 (5)	NS
		End of exercise	92 (5)***	113 (6)***	<0.02
HR (beats/min)	Rest		70 (8)	72 (3)	NS
	Standing		82 (6)**	87 (4)***	NS
	End of exercise		121 (9)***	139 (5)***	NS
Duration of exercise (min)			5.5 (0.5)	6.8 (0.8)	NS

*, **, *** p < 0.05, p < 0.01, p < 0.001, respectively for rest v standing

, *, p < 0.01, p < 0.001, respectively for standing v end of exercise.

BP, blood pressure; HR, heart rate.

COLD PRESSOR TEST

We examined whether the impaired response of blood pressure to exercise in patients in group 1 was caused by non-specific abnormalities in neurogenic vasoconstriction by comparing the blood pressure response to the cold pressor test in six patients from each group. The patients lay quietly for 15 minutes before testing. When the basal blood pressure was

stable they put a hand in ice water for one minute. Blood pressure was measured by a sphygmomanometer before and at the end of the cold stimulus.

STATISTICAL ANALYSIS

All data were expressed as mean (SEM). Statistical analysis was performed by the analysis of variance, F test, t test, and paired t test where indicated. A p value of <0.05 was regarded as significant.

Table 3 Haemodynamic responses to ergometer exercise

Variable		Group 1 (n = 8)	Group 2 (n = 10)	p value (group 1 vs group 2)
HR (beats/min):	R	73 (4)	83 (4)	NS
	EX	88 (5)**	100 (3)***	<0.05
	Δ	15 (3)	17 (2)	NS
PAWP (mm Hg)	R	13 (2)	11 (2)	NS
	EX	18 (3)*	18 (3)**	NS
	Δ	6 (2)	6 (1)	NS
SAP (mm Hg)	R	141 (5)	129 (7)	NS
	EX	142 (7)	153 (8)***	NS
	Δ	1 (5)	23 (4)	<0.01
DAP (mm Hg)	R	79 (4)	77 (5)	NS
	EX	79 (3)	85 (5)*	NS
	Δ	0 (2)	8 (3)	Δ 0.05
MAP (mm Hg):	R	106 (4)	100 (5)	NS
	EX	105 (4)	115 (6)***	NS
	Δ	-1 (2)	14 (3)	<0.001
CI (l/min/m ²):	R	3.9 (0.2)	4.1 (0.3)	NS
	EX	4.6 (0.3)**	5.2 (0.3)**	NS
	Δ	0.7 (0.2)	1.1 (0.3)	NS
SVRI (mm Hg/l/min/m ²):	R	28.0 (1.6)	25.4 (2.3)	NS
	EX	23.6 (1.7)**	22.8 (2.1)*	NS
	Δ	-4.5 (1.2)	-2.6 (1.0)	NS
V̇O ₂ (ml/min):	R	239 (11)	232 (20)	NS
	EX	500 (39)***	580 (38)***	NS
	EX/R(%)	209 (15)	580 (38)***	NS
Δ		261 (35)	348 (32)	NS

*, **, *** p < 0.05, p < 0.01, p < 0.001 respectively for rest v exercise

HR, heart rate; PAWP, pulmonary artery wedge pressure; SAP, systolic aortic pressure; DAP, diastolic aortic pressure; MAP, mean aortic pressure; CI, cardiac index; SVRI, systemic vascular resistance index; V̇O₂, oxygen consumption; R = at rest; EX, during exercise; Δ, difference between R and EX; NS, not significant.

Results

BASELINE VALUES (TABLE 1)

Age and the frequency of a history of myocardial infarction were similar in the two groups. The extent and distribution of coronary artery disease were also similar, as were resting left ventricular end diastolic pressure and left ventricular ejection fraction.

RESPONSES TO TREADMILL EXERCISE (TABLE 2)

Systolic, diastolic, and mean blood pressure and heart rate in recumbent and standing patients before the start of exercise testing were similar in the two groups. There was no orthostatic hypotension in either group. During treadmill exercise, systolic and mean blood pressure increased (p < 0.01 for each) in group 2 whereas in group 1 systolic blood pressure did not change and diastolic and mean blood pressure decreased (p < 0.001, and p < 0.01 respectively). The duration of exercise testing did not differ in the two groups.

RESPONSES TO ERGOMETER EXERCISE (TABLE 3)

Measurements of heart rate; pulmonary artery wedge pressure; systolic, diastolic, and mean blood pressure; cardiac index; systemic vascular resistance index; and oxygen consumption were similar at rest in the two groups. During ergometer exercise, heart

Table 4 Response of forearm blood flow and forearm vascular resistance to ergometer exercise

		Group 1 (n = 8)	Group 2 (n = 10)	p value (group 1 vs group 2)
FoBF (ml/min/100 g.)	R	4.2 (0.5)	5.7 (0.7)	NS
	EX	3.7 (0.5)	3.9 (0.5)***	NS
	Δ	-0.5 (0.3)	-1.8 (0.4)	<0.01
FoVR units)	R	27.5 (2.7)	20.6 (3.3)	NS
	EX	30.2 (2.4)	33.8 (4.9)**	NS
	Δ	2.7 (1.4)	13.2 (2.8)	<0.01

, * $p < 0.01$, $p < 0.001$ respectively, for rest vs exercise. FoBF, forearm blood flow; FoVR, forearm vascular resistance; R, at rest; EX, during exercise; Δ, difference between rest and exercise.

rate, pulmonary artery wedge pressure, cardiac index, and oxygen consumption increased and systemic vascular resistance index decreased in both groups. Systolic, diastolic, and mean blood pressure increased during ergometer exercise in group 2 whereas they did not change in group 1. The sizes of the changes in pulmonary artery wedge pressure, cardiac index, systemic vascular resistance index, and oxygen consumption induced by exercise were not significantly different in the two groups. Heart rate during exercise was higher in group 2 than in group 1 but the size of the increase in heart rate induced by exercise was not different in the two groups.

CHANGES IN FOREARM VASCULAR RESISTANCE DURING ERGOMETER EXERCISE (TABLE 4)

Forearm blood flow decreased and forearm vascular resistance increased during leg exercise on a bicycle ergometer in group 2 patients but they did not

Table 5 Response of systolic, diastolic, and mean blood pressure to the cold pressor test

		Group 1	Group 2	p value (group 1 vs group 2)
SBP (mm Hg)	Before	133(7)	117(8)	NS
	CPT	150(9)**	134(8)***	NS
	Δ	17(3)	17(2)	NS
DBP (mm Hg):	Before	77(4)	72(7)	NS
	CPT	90(4)**	87(6)	NS
	Δ	13(3)	15(3)	NS
MBP (mm Hg)	Before	96(4)	87(7)	NS
	CPT	110(5)**	103(7)	NS
	Δ	14(2)	16(2)	NS

, * $p < 0.01$, $p < 0.001$ respectively for values before and after the cold pressor test.

SBP, DBP, MBP, systolic, diastolic and mean blood pressure, respectively, CPT, cold pressor test; Δ, difference between the values before and during the cold pressor test.

significantly change in group 1 patients. The sizes of changes in forearm blood flow and forearm vascular resistance were significantly different in the two groups. There was a positive correlation between the increases in mean blood pressure and increases in forearm vascular resistance during ergometer exercise ($y = 0.59x + 4.14$, $r = 0.71$, $p < 0.01$) (figure).

BLOOD PRESSURE RESPONSES TO THE COLD PRESSOR TEST (TABLE 5)

Systolic, diastolic, and mean blood pressure increased with the cold pressor test in both groups. The increases in blood pressure with the cold pressor test were not significantly different in the two groups.

Discussion

From the results of this study we conclude that the impaired blood pressure response to ergometer exercise in group 1 was not the result of a failure to increase cardiac output and that the impaired blood pressure response to ergometer exercise was associated with less vasoconstriction in the non-exercising forearm. There was a positive correlation between the magnitude of reflex vasoconstriction in non-exercising forearm and the rise in blood pressure during ergometer exercise. These results suggest that impaired reflex vasoconstriction in non-exercising muscles may have contributed to abnormal blood pressure response to ergometer exercise in these patients with coronary artery disease.

Other cardiac disorders including obstructive valvular disease, particularly aortic and mitral stenosis, and severe left ventricular dysfunction may cause exertional hypotension. Exertional hypotension may

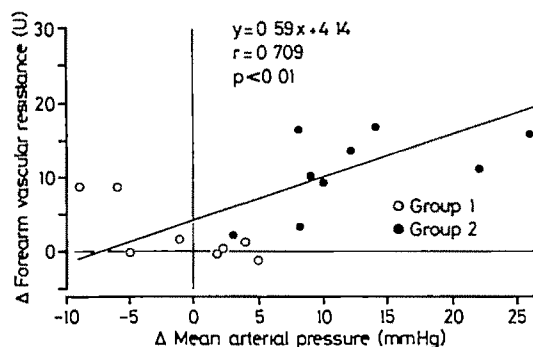


Figure Relation between increase in mean blood pressure (x) and increase in forearm vascular resistance during ergometer exercise (y). There was a positive correlation between them.

occur in association with exercise induced arrhythmias. However, none of these abnormalities was present in our patients. Drugs such as β blockers can also cause exertional hypotension.¹⁰ Our patients were not on β blockers. Three patients in group 1 were on isosorbide dinitrate in combination with diltiazem or nifedipine. These drugs do not reduce the increase in blood pressure that occurs with exercise.^{11,12} Three patients in group 2 were on similar drugs but did not have impaired blood pressure response to exercise. Also it has been shown that exertional hypotension can occur in normal subjects at the beginning of exercise^{4,13} or during maximal exhaustive exercise.^{14,15} In our patients blood pressure was measured after an average of 5.5 minutes of submaximal exercise. Thus we consider that the impaired blood pressure response to exercise in our patients was probably related to coronary artery disease. Furthermore, blood pressure responses to the cold pressor test were similar in the two groups, which suggests that impaired blood pressure response to exercise in group 1 was unlikely to have been the result of non-specific autonomic dysfunction.

In this study the patients had two types of exercise testing. The patients were divided into two groups on the basis of the blood pressure response to treadmill exercise as in previous studies^{10,13} and haemodynamic and forearm vascular responses to exercise were examined during supine leg exercise with a bicycle ergometer. This protocol was chosen because reliable measurements of forearm blood flow in a resting forearm were possible only with patients in a supine position. The workload on the ergometer was smaller than that with a treadmill so that all patients could exercise for six minutes and all the measurements could be completed. There were some differences in blood pressure responses between treadmill and ergometer exercise in groups 1 and 2 (tables 1 and 2), which were likely to have resulted from differences in workloads and body position. Patients with impaired blood pressure responses to treadmill exercise also had impaired blood pressure response to less demanding exercise on a bicycle ergometer.

We found that the increase in cardiac output during ergometer exercise was not significantly different in the two groups despite different blood pressure responses. Failure to increase cardiac output during exercise did not account for the impaired blood pressure response during exercise in group 1. The increases in pulmonary artery wedge pressure during ergometer exercise also were similar in the two groups, suggesting that the development of acute left ventricular pump failure in group 1 was unlikely.

Thompson and Kelemen reported that patients who had hypotension accompanying angina during

treadmill exercise did not develop hypotension with pacing induced angina in the supine position.¹ These results suggest that impaired blood pressure response to exercise in their patients was unlikely to have been the result of the development of myocardial ischaemia itself. It was more likely to have been related to altered control of vascular resistance during exercise. The results of our study are consistent with this view. We found that there was less reflex vasoconstriction in the forearm during leg exercise with an ergometer in patients with impaired blood pressure response to an ergometer and to treadmill exercise than in patients who had a normal hypertensive response. Furthermore, there was a positive correlation between the increase in blood pressure and the degree of reflex forearm vasoconstriction during ergometer exercise. We believe that impaired reflex vasoconstriction in non-exercising muscles might have contributed to impaired blood pressure response to exercise.

We cannot be certain what mechanisms impaired reflex vasoconstriction in the forearm during leg exercise in patients who had impaired blood pressure response to exercise. Reflex sympathetic activation during exercise may be mediated by a somatic receptor reflex originating in exercising muscles.^{16,17} It also has been shown that reflex sympathetic activation mediated by a somatic receptor reflex may be attenuated by stimulation of the cardiac receptors.^{18,19} Thus an attenuation of reflex forearm vasoconstriction in patients who had impaired blood pressure response to exercise might have resulted from impaired somatic receptor reflex during exercise or from greater activation of the cardiac receptors. To examine the possibility that activation of the cardiac receptors during exercise might have been greater in patients with an impaired blood pressure response than in those with a normal hypertensive response, we examined the increase in pulmonary artery wedge pressure during exercise and the distribution of coronary artery disease. Cardiac receptors are stimulated by an increase in left ventricular diastolic pressure²⁰ and there are more of them in the inferior wall of the left ventricle.^{21,22} But the increase in pulmonary artery wedge pressure and the distribution of coronary artery disease were similar in the two groups. Further studies are needed to clarify the mechanisms that impair reflex forearm vasoconstriction during leg exercise in patients with impaired blood pressure response to exercise.

In summary, patients who had impaired blood pressure response to treadmill exercise also showed an impaired blood pressure response to less strenuous exercise on an ergometer. The impaired blood pressure response to ergometer exercise was not accounted for by a failure to increase cardiac

Table 1 Characterisation of study groups (mean (SD))

Characteristic	Endurance athletes (n = 20)	Controls (n = 20)	p value
Age (yr)	56 (7)	56 (7)	NS
Resting heart rate (beats/min)	51 (7)	72 (10)	<0.001
Systolic blood pressure (mm Hg)	125 (15)	135 (23)	<0.01
Maximum treadmill exercise time (min)	19 (4)	16 (2)	<0.01
Height (m)	1.75 (0.048)	1.74 (0.079)	NS
Weight (kg)	64 (5)	74 (8)	<0.01
Body mass index (Quetelet kg/cm ² × 10 ³)	2.24 (0.01)	2.45 (0.25)	<0.01
Running experience (yr)	36 (7) (28-50)	—	—
Miles/week	47 (23) (25-110)	—	—
Best marathon time (min)	175 (23) (2:25-3:40)	—	—

at least two hours rest, Holter monitoring was performed with the Medilog 4000 (MARS) ambulatory electrocardiogram recorder (Oxford Medical Systems, Oxford).

This recorder processes each beat/complex in real time and stores the analysed data on a cassette tape. The information was retrieved by the Medilog MARS Replay System (Oxford Medical Systems, Oxford).

After careful skin preparation with an abrasive paste, and shaving if necessary, five electrodes (Medicotest) were applied to the chest wall to produce a recording of lead CM5 and a modified lead II. An impedance meter was then used to ensure that the resistance between each electrode was <5 kΩ and surgical tape was used to secure the leads to the chest wall with stress loops to reduce motion artefact. The recorder was worn at the patient's side on a belt. A 1 mV test signal was then recorded and this was used by the system to calibrate analysed data.

Holter monitoring was continued for 48 hours. For the first 24 hours the patient was instructed to follow his normal daily routine without running or vigorous exercise and to record any symptoms or events in a diary. During the second 24 hours the athletes were asked to run for 40 minutes at their normal training pace. Before they left the laboratory the electrocardiographic waveform and magnitude being recorded were confirmed on a conventional writer to ensure a satisfactory recording. At the end of each recording the cassette was transferred to the Medilog MARS replay system which generates a comprehensive report via a microdot printer. A full 24 hour recording was obtained for every man and if important abnormalities were found appropriate times were searched at conventional paper speed (25 mm/

Table 2 Resting electrocardiography

	Athletes	Controls	p
SV1 + RV5	28 (7.2)	25 (7.8)	<0.05
PR	0.20 (0.04)	0.18 (0.03)	<0.05
QTc	0.42 (0.027)	0.42 (0.027)	NS
QRS	0.10 (0.01)	0.10 (0.01)	NS

PR, QRS intervals, and QTc derivative measured in seconds. All data given are mean (SD).

s). Mean nocturnal heart rate was derived from the mean of the hourly rates between midnight and 6 am when the men were in bed. Maximum and minimum heart rates were recorded from the average RR interval over four complexes. An asystolic pause was defined as asystole lasting >1.5 seconds and 1.9 times longer than the average RR interval of the four previous complexes. Ventricular tachycardia was regarded as being present if three or more consecutive premature ventricular contractions occurred at a rate exceeding 110 beats/min. If the rate was less than 110 beats/min then idioventricular rhythm was regarded as being present. Premature ventricular contractions were classified according to the Lown grading system.¹⁹

Results

RESTING ELECTROCARDIOGRAMS

At rest two athletes had evidence of both second (Mobitz type II) and third degree heart block (QRS duration 0.08 and 0.10 s respectively). Four athletes and three controls satisfied voltage criteria for left ventricular hypertrophy, the athletes having a greater mean voltage than the controls (table 2). There was a significantly prolonged PR interval in the athletes ($p < 0.05$) but no difference in the QTc derivative or QRS duration.

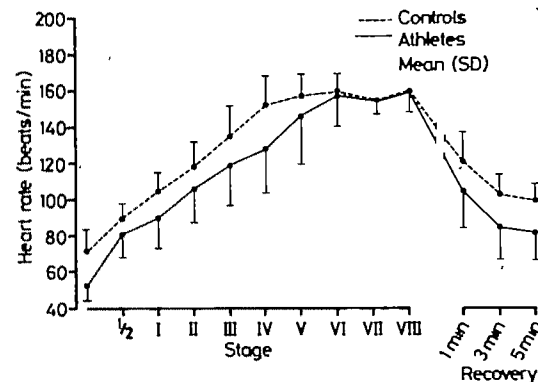


Fig 1 Heart rate response to treadmill exercise test and in the immediate post-exercise recovery period.

EXERCISE ELECTROCARDIOGRAPHY

The mean (SD) maximum treadmill exercise time was 19 (4) minutes in athletes and 16 (2) minutes in the control group ($p < 0.01$). As a group the athletes were able to perform more work at a lower heart rate. Twelve athletes but only four controls surpassed stage V of the protocol. Figure 1 shows the heart rate responses to treadmill exercise and fig 2 the exercise times. Four athletes but no controls had > 2 mm of downsloping ST segment depression during exercise and one other had frequent unifocal premature ventricular complexes after exercise. Two athletes who developed ST segment depression were offered coronary angiography, one because of the subsequent development of chest pain and one because of the concurrent finding of complete heart block with profound bradycardia (< 25 beats/min). Both arteriograms were entirely normal. (Figure 3 shows the exercise electrocardiograms.)

AMBULATORY ELECTROCARDIOGRAPHY

The athletes had a consistently lower heart rate at all times of the day (table 3). Eight athletes but only one control had a profound sinus bradycardia (< 35 beats/min); the lowest heart rate in an athlete was 17 beats/min recorded at 3 am while he was asleep. The circadian variation of heart rate was maintained in athletes despite the bradycardia (fig 4). Eight athletes and two controls had evidence of asystolic pauses (> 1.5 s); one of them had 846 episodes. This individual had pauses ranging from 1.8 to 15 seconds and had evidence of first, second (2:1 Mobitz type II), and third degree atrioventricular block at various times of the day. This individual was not prepared to stop his endurance running and because we believed that he might be at risk of cerebrovascular accident²⁰ or even sudden death we decided to implant a

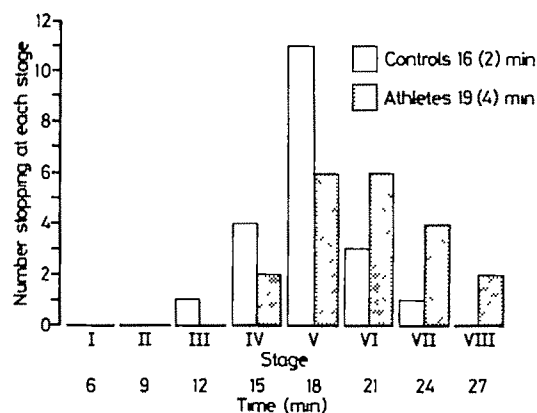


Fig 2 Exercise times on treadmill according to the stage at which an individual stopped because of fatigue or breathlessness.

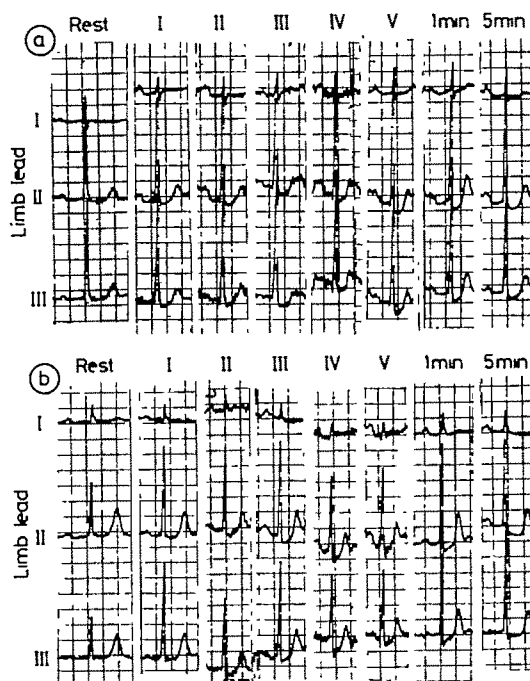


Fig 3 Exercise electrocardiograms of two of the four athletes who had an "ischaemic response" and who were offered coronary arteriography. The electrocardiograms show a progression through the stages of a Bruce protocol and the immediate post-exercise recovery period.

permanent dual chamber pacemaker (Pacesetter AFP 283). Interestingly, although the patient did not report any symptoms before implantation, he remarked that he felt more energetic afterwards and was able to reduce his time for a 10 mile run by several minutes. Six athletes had a prolonged PR interval (> 0.22 s), four had second degree atrioventricular block, and three had complete or third degree heart block. Apart from the two men who had four episodes of asystole between them, no conduction abnormalities were found in the control group. Most asystolic pauses occurred at night (fig 5).

Two of the athletes with complete heart block also had an abnormal electrocardiographic response to

Table 3 Heart rates derived from continuous 24 hour electrocardiography (mean (SD))

Heart rate	Athletes	Controls	p
Mean 24 hour	59 (8.3)	74 (9.3)	< 0.001
Minimum	37 (7.8)	47 (6.0)	< 0.01
Maximum	121 (21.9)	144 (18.6)	
Mean daytime	61 (8.2)	76 (9.5)	< 0.001
Mean nocturnal	51 (8.5)	66 (13.2)	< 0.001

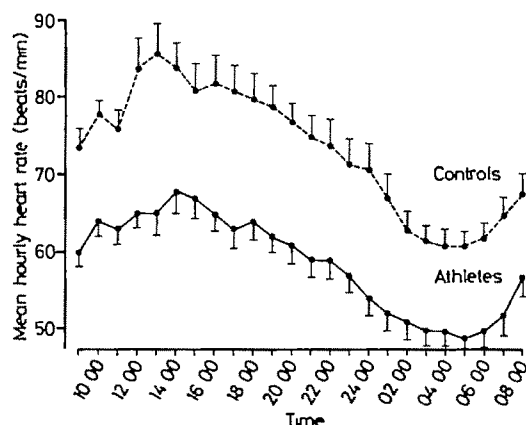


Fig 4 Twenty four hour trend of heart rate in athletes and controls (mean hourly rate (SE)).

treadmill exercise. As previously mentioned one of them underwent coronary angiography with a normal result. During sedentary activities 15 of the 20 athletes had at least one premature ventricular contraction per 24 hours compared with 18 of the controls, but only four athletes and four controls had >50 premature ventricular contractions per 24 hours. One athlete had 1652 in 24 hours. This man had multifocal extrasystoles normally distributed throughout 24 hours including couplets and a short episode of ventricular trigeminy. In addition he also had a short episode of paroxysmal atrial tachycardia. When his data were excluded, there was no significant difference between the total number of premature ventricular contractions occurring in both groups (380 v 370) (table 4).

Two controls had episodes of self terminating ventricular tachycardia, one of 18 and the other of 60 complexes. The premature ventricular contractions

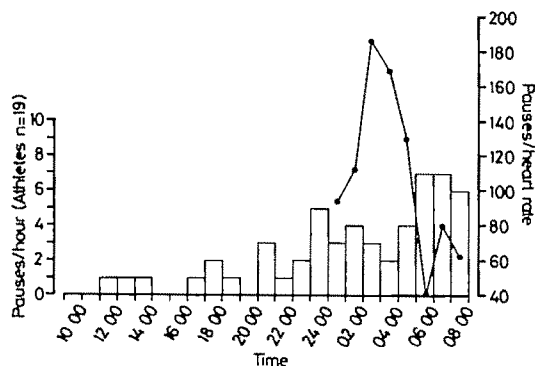


Fig 5 Frequency distribution of asystolic pauses throughout 24 hours. Solid line shows the distribution in a man with 846 pauses in 24 hours, which only occurred between the hours of 0100 and 0800.

Table 4 Classification of ventricular ectopic activity in athletes and controls

	Athletes		Controls	
	No	% of total	No	% of total
<i>Low grade</i>				
No PVCs (0)	5	25	2	10
Occasional PVCs 1/min (1a)	12	60	18	90
Occasional PVCs (1/min (1b)	1	5	0	0
Frequent PVCs (2)*	2	10	2	10
Multifocal PVCs (3)	3	15	1	5
Repetitive PVCs in couplets (4a)	2	10	1	5
Repetitive PVCs in salvos (4b)	0	0	2	10
Early PVCs (R on T) (5)	1	5	0	0

* Ventricular bigeminy and trigeminy are grouped under Low grade 2 PVC, premature ventricular contractions.

were mostly unifocal and occurred sporadically throughout 24 hours (fig 6). During the second period of 24 hours, in which the athletes completed a 40 minute road run, 11 of 17 athletes (the recordings on three athletes were unsuitable for analysis because of electrode displacement) had scattered premature ventricular contractions; most of these were isolated and unifocal (Low grade 1a in ten cases and Low grade 1b in one case). One individual had evidence of R on T (RR/QT < 0.85) during running (Low grade 5) but, in general, training did not appear to provoke an increased frequency of ventricular extrasystoles. The maximum heart rate achieved during outdoor running was 162 (18) beats/min (range 122–196), equivalent to a predicted maximum heart rate for the group of 99%. All patterns of atrioventricular block disappeared during exercise and there was no correlation between the presence of premature ventricular contractions and an abnormal electrocardiographic response to treadmill exercise.

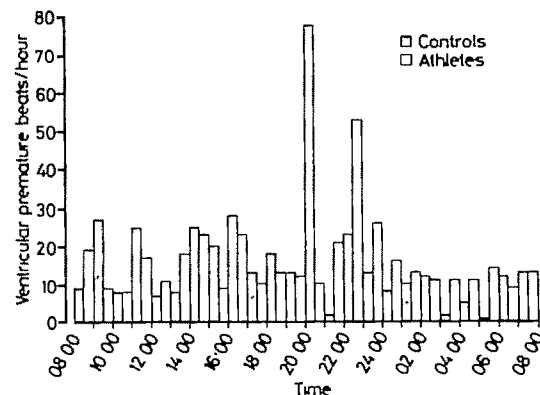


Fig 6 Frequency histogram of PVCs in athletes and controls throughout 24 hours (excluding athletes with >1600 PVCs per 24 hours).

Discussion

We compared athletes with a group of healthy control subjects who participated in light physical activity. All the athletes trained exclusively by distance running and did not use weight training or resistance exercise; thus any confusion with the effects of anaerobic or power exercise (including isometric exercise) was avoided. The controls were chosen from a group of volunteers. Clearly, habitual long distance runners are very difficult to match with a control population. They tend to be very lean, from high educational and socioeconomic groups, and are conscious of their diet and health. The control group in this study was not an inactive slothful cohort of middle aged men and this is reflected in the mean treadmill exercise time of 16 minutes. So we believe that our control group was as closely matched as possible.

Athlete's bradycardia is a well documented phenomenon and has been investigated in young athletes by several groups.¹⁰⁻¹⁵ Like us, Viitsalo *et al* found that despite the bradycardia, circadian variation of heart rate was maintained.¹⁴ The cause of bradycardia in athletic subjects is uncertain. Most evidence suggests that the sinoatrial node and atrioventricular nodes are suppressed by an increase in vagal tone, which can be abolished by atropine or stopping training.^{8,21} However, increased vagal tone may only be partly responsible because studies of surgical denervation and pharmacological denervation (atropine plus propranolol) have shown the bradycardia to be independent of vagal tone.^{22,23} Thus the intrinsic heart rate is lower.

Although the bradycardia seen in athletes is currently recognised as a benign adaptation, it has been associated with unexplained cerebrovascular accidents²⁰ and becomes more notable when associated with atrioventricular block patterns. It is possible that continuous habitual vigorous exercise throughout life may result in a bradycardia which, rather than being adaptive, has been modified into a condition resembling the sick sinus syndrome. It is for this reason that one of the subjects in the present study, who also had prolonged periods of asystole, had implantation of a permanent pacemaker. Until follow up studies of patients with exercise induced bradycardia and atrioventricular block have been published, cardiologists will have no firm guidelines on the management of this condition. If an athlete does not wish to stop exercising, then pacemaker implantation may need to be considered in severe cases, even in the absence of symptoms.

Several studies have noted the presence of asystolic pauses in athletic populations.^{19,12,14,16} Typically these have lasted from 1.6 to 2.8 s. We have been unable to

find any other reports of pauses of up to 15 seconds in the absence of symptoms. Ector *et al* studied 16 sportsmen who presented with syncope.¹⁶ Half of them became symptom free on stopping training, although another seven required implantation of a permanent pacemaker. Thus stopping training does not always resolve the problem. Although first degree and, to a lesser extent, second degree atrioventricular block has been found in younger athletes^{10,12,14,15} complete heart block in a symptom free normal or athletic population is exceedingly rare. In athletes the frequency of first degree heart block varies from 5% to 55%^{8,12,14,15} but is typically around 20%. Second degree atrioventricular block (Mobitz type II and Wenckebach) is less common and is found in 13-22% of athletes.^{12,14-16} Thus the frequency of first and second degree atrioventricular block (Mobitz type II) found in this study is similar to that in younger athletes but none of the earlier studies reported complete heart block, which occurred in three of our athletes.¹⁰⁻¹⁵ The occurrence of block patterns in athletes is probably related to increased vagal tone, because resolution can occur during exercise. However, in some veteran athletes it may coexist with the sick sinus syndrome and thus lead to profound bradycardia and symptoms. The resting electrocardiograms of the athletes in this study were unhelpful in identifying all those with atrioventricular block, although complete heart block was found in two men.

In contrast with other sports, which exert a predominantly pressure overload on the left ventricle, running induces volume overload. Thus only four of 20 athletes (20%) (S1 + R5 mean = 28 mm) satisfied voltage criteria for left ventricular hypertrophy compared with 101 (35%) of 289 professional American Football players trained on power and resistance exercise⁹ (S1 + R5 mean = 37 mm). Although the QTc derivative may be prolonged in some athletes^{24,25} we did not find any difference between our runners and controls.

Four athletes in this study had an exercise electrocardiogram that satisfied the criteria for ischaemia (greater than 1 mm downward sloping ST segment depression occurring 0.08 seconds after the J point)—two of them had entirely normal coronary arteriograms. This is more than would be expected in a normal symptom free population. Balady *et al* found that 13% of power trained athletes had ST segment depression on resting electrocardiograms⁹ and Pantano and Orieig describes three well trained runners who had an ischaemic response to treadmill exercise but who had normal thallium-201 myocardial perfusion scans.¹¹ The reason for this false positive response is not clear. It has been suggested that athletes' ventricles repolarise in a non-homo-

geneous fashion with repolarisation of the epicardium occurring first.²⁶ The asymmetry of repolarisation may be related to reduced sympathetic tone.²⁷ Although two previous studies in healthy middle aged men suggested that long term participation in exercise results in fewer premature ventricular contractions,^{28,29} there was no difference between the groups in the frequency of premature ventricular contractions in this study. The frequency (only 20% in each group had >50 premature ventricular contractions per 24 hours) was similar to that reported in younger athletes^{10,12,14} and unlike Pantano and Orieig¹¹ we did not find that the frequency of premature ventricular contractions was increased during out of hospital exercise training. In the symptom free athlete it is highly probable that infrequent premature ventricular contractions are a normal finding that should not precipitate further investigation.

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SUMMARY The optimal atrioventricular delay at rest and during exercise was investigated in nine patients with heart block and implanted dual chamber pacemakers. All patients studied had normal left ventricular function and a normal sinus node rate response to exercise. Cardiac output was measured by continuous wave Doppler and was calculated as the product of stroke distance measured by Doppler at the left ventricular outflow, aortic root area measured by M mode echocardiography, and heart rate. Pacemakers were programmed in the DDD mode. Cardiac output was measured with the patient at rest while supine and while erect and at the peak of submaximal exercise (the end of stage 1 of the Bruce protocol) with the pacemakers programmed to the following atrioventricular intervals: 75–80 ms, 100–110 ms, 140–150 ms, and 200 ms. During exercise the basic pacing rate was programmed to 70 beats/min. Cardiac output at rest while supine and erect was greatest with an atrioventricular delay of 140–150 ms and it was significantly higher than that with an atrioventricular delay of 75–80 ms. On average there was a 31% decrease in cardiac output when patients stood up. During treadmill exercise, however, cardiac output was greatest when the atrioventricular delay was 75–80 ms, and this was significantly higher than the cardiac output with atrioventricular delays of 150 and 200 ms. During exercise 1:1 atrioventricular relations were maintained in all patients at all atrioventricular intervals.

In patients with atrioventricular sequential pacemakers cardiac output at rest is greatest with an atrioventricular delay of 140–150 ms but during exercise the optimal atrioventricular delay is shorter. Rate modulation of the atrioventricular interval may improve the haemodynamic response and possibly exercise tolerance in patients with dual chamber pacemakers.

The importance of an appropriately timed atrial contraction in maintaining optimal cardiac output is now well established in patients with normal and abnormal ventricular function.¹⁻⁴ The temporal relation between atrial and ventricular systole is a determinant of ventricular performance because this interval influences both ventricular filling⁵ and closure of the atrioventricular valve.^{6,7} Several invasive⁸ and non-invasive⁹⁻¹² studies have reported that an atrioventricular interval of 150–200 ms is associated with maximal cardiac output at rest. We

evaluated the optimal atrioventricular delay on exercise in patients with normal left ventricular function. Cardiac output was measured non-invasively by continuous wave Doppler techniques.

Patients and methods

Thirteen patients with dual chamber pacemakers and complete heart block were considered for the study. All had normal left ventricular function (mean ejection fraction 63.8 (7.9)%) and no evidence of valvar heart disease on M mode echocardiography. To assess their suitability for inclusion patients underwent a three minute treadmill exercise test (treadmill speed = 2.7 km/h and gradient = 10%). Doppler signals from the aorta were recorded at rest

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Table 1 Clinical and pacemaker data of the patients

Patient	Age (yr)	Sex	Pacemaker	Duration of implantation (yr)	EF %
1	40	M	Teletronics(Autima II)*	5	53.3
2	58	M	Teletronics(Autima II)	2	44.6
3	66	M	Cordis(Sequior III)†	3	71.0
4	59	F	Teletronics(Autima II)	2	75.5
5	22	F	Medtronic (Symbios 7005C)‡	1	67.9
6	70	M	Medtronic (Symbios 7005C)	1	62
7	53	M	Teletronics(Autima II)	1	59
8	43	M	Medtronic (Symbios 7005C)	1	56.8
9	46	M	Cordis(Sequior III)	4	62

*Teletronics, Sydney, Australia, †Cordis Corporation, Miami, Florida, USA, ‡Medtronic, Inc., Minneapolis, USA
EF, left ventricular ejection fraction measured by M mode echocardiography.

and during exercise. Four patients were excluded from the study—two with unsatisfactory Doppler signals, one with an inadequate sinus node rate response to exercise (atrial rate of <85 beats/minute at end of three minutes exercise) and one because 1:1 atrioventricular conduction developed on exercise. Table 1 shows selected clinical and pacemaker data of the nine patients (average age 53) included in the complete study.

CARDIAC OUTPUTS MEASURED BY DOPPLER

Cardiac output was measured by a continuous wave Doppler system (Quinton Exerdop). This "stand alone" continuous wave Doppler equipment transmits a 3 MHz signal through a 10 mm diameter crystal. A proprietary circuit uses frequency analysis to process the reflected signal. The signal is sampled every 5 ms. Only signals coming towards the transducer and at least 10 decibels above the background noise are processed. A dedicated computer calculates the flow velocity by integrating the area under the curve (systolic velocity integral) using a modified rectangular algorithm. An average of at least 10 consecutive beats was used to calculate the cardiac output at any stage of the experiment. Cardiac output was calculated as the systolic velocity integral $\times$ aortic root area $\times$ heart rate. The aortic root area was calculated from the diameter of the root of the ascending aorta measured by M mode echocardiography. The measurement was taken just above the level of the aortic cusps. The heart rate used for the calculation of cardiac output was averaged from 10 beats recorded simultaneously with the Doppler recordings. In previous studies cardiac output measured in this way has been shown to correlate well with measurement of cardiac output by the Fick¹³ and thermodilution methods¹⁴ (correlation coefficient 0.80–0.96).

The feasibility of Doppler techniques for measuring cardiac haemodynamic function during exercise is now established.^{15,16} The transducer used is small and the probe sufficiently angled so that the ultrasound signal can be easily directed parallel or nearly parallel to the blood flow in the ascending aorta. Because the transducer is small it can easily be maintained in a stable recording position during exercise and has been previously used satisfactorily at our centre to assess the haemodynamic function of post-infarction patients during exercise.¹⁵ Because it is non-invasive, this technique of measuring cardiac output is well suited for repeated assessment of patients with implanted devices.

PACEMAKER SETTINGS

During the study the pacemakers were programmed to the DDD mode. Cardiac output was measured at rest at four atrioventricular intervals with the basic pacing rate programmed to 70 beats/minute and 90 beats/minute. At each rate the atrioventricular interval was randomly programmed to 75, 100, 150, and 200 ms. Teletronics pacemakers have a different range of programmable atrioventricular delays—the corresponding atrioventricular delays in patients with these pacemakers were 80, 110, 140, and 200 ms. For uniformity, hereafter, these are also referred to as 75, 100, 150, and 200 ms. After each reprogramming, the atrioventricular interval was confirmed by electrocardiography.

During exercise the basic pacing rate was programmed to 70 beats/minute. At each setting of the atrioventricular interval Doppler measurements were made five minutes after standing and at the peak of treadmill exercises. The operator making the Doppler recordings was unaware of the pacemaker settings.

EXERCISE PROTOCOL

Patients were exercised on a treadmill for three minutes at settings identical to Bruce protocol stage 1 (gradient = 10%, speed = 2.7 km/h.¹⁷ Doppler measurements were made during the last 15 s of exercise. Faster treadmill walking speed was not used because it caused unacceptable background noise on Doppler recordings.

Table 2 Mean (SD) heart rate (beats/minute) at different stages of the protocol

Atrioventricular interval	Supine	Standing	Peak exercise
75 ms	70.8 (2)	70.9 (3)	102 (9)
100 ms	70.6 (2)	70.6 (2)	101.6 (10)
150 ms	70.6 (2)	71.2 (2)	101.5 (9)
200 ms	70.6 (2)	71.4 (3)	101.6 (7.9)

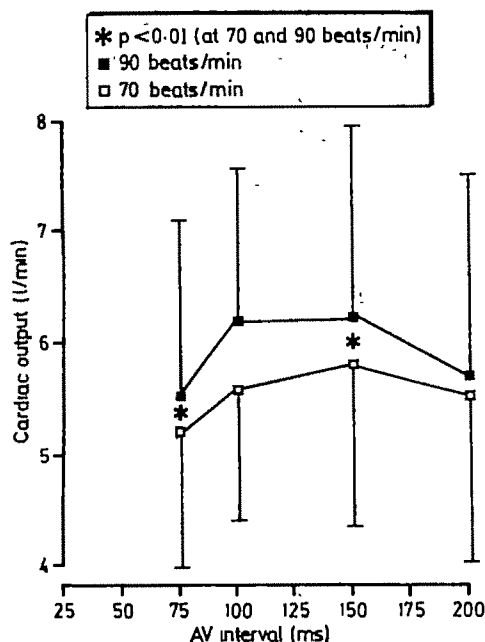


Fig 1 Comparison of mean (SD) cardiac output at the four atrioventricular delays with basic pacing rates programmed at 70 and 90 beats/minutes in resting supine patients. Cardiac output was significantly higher at an AV interval of 150 ms compared with an interval of 75 ms. This result was true at both pacing rates.

STATISTICAL METHOD

All values were expressed as group mean (SD). Paired *t* tests were used to measure statistical differences between heart rates and between cardiac outputs at various atrioventricular intervals. A *p* value of <0.05 was regarded as significant.

Results

At rest, with the basic pacing rate programmed to 70 beats/minute, four patients were pacing in both the atrium and ventricle, while five were tracking the P waves and pacing in the ventricle. Table 2 shows the mean pacing rates (SD) of the group at different stages of the protocol. The pacing rates at rest and during exercise at each of the four atrioventricular intervals were not significantly different. With the pacing rate programmed to 90 beats/minute, cardiac outputs at atrioventricular delays of 75, 100, 150, and 200 ms were 5.55 (1.5), 6.29 (1.7), 6.42 (1.8), and 5.88 (1.6) l/min respectively (fig 1). Cardiac output was significantly greater ($p < 0.05$) with an atrioventricular interval of 150 ms than with one of 75 ms¹⁸. No other difference was significant. Before exercise when the patient was supine with the basic

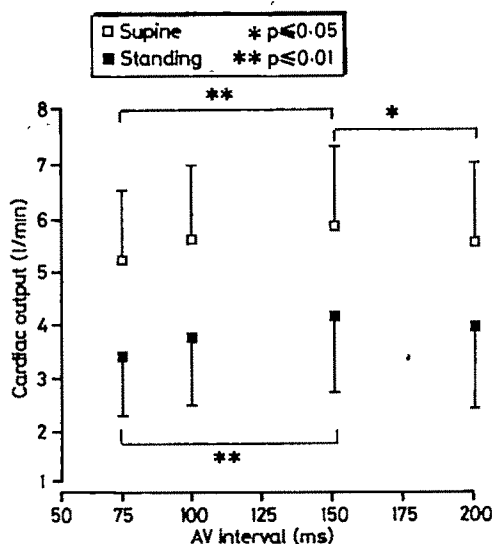


Fig 2 Changes in mean (SD) cardiac output at rest when the patient stood up. With all four atrioventricular delays there was a similar fall in cardiac output (mean 31%).

pacing rate programmed to 70 beats/minute cardiac output was again greatest with an atrioventricular interval of 150 ms (5.81 (1.5) l/min) (fig 2), and it was significantly lower at atrioventricular intervals of 75 (5.20 (1.3) l/min, $p < 0.01$) and 200 ms (5.51 (1.5) l/min, $p < 0.05$). Whatever the atrioventricular delay, there was a 31% decrease in cardiac output on standing (fig 2). Cardiac output on standing was again greatest with an atrioventricular delay of 150 ms (4.13 (1.4) l/min), and this was significantly higher than the cardiac output with an atrioventricular delay of 75 ms (3.40 (1.02) l/min, $p < 0.01$).

The greatest cardiac output during exercise was seen with an atrioventricular delay of 75 ms (8.26 (1.1) l/min); this was significantly higher than cardiac outputs at atrioventricular intervals of 150 and 200 ms (7.46 (0.9) l/min ($p < 0.05$) and 7.85 (1.1) l/min ($p < 0.05$) respectively). Thus with the mild exercise used in our protocol the greatest increase in cardiac output was seen with an atrioventricular delay of 75 ms (fig 3). These changes in cardiac output between atrioventricular intervals are unrelated to changes in pacing rate because the increase in heart rate on exercise at all four atrioventricular intervals was virtually identical (table 2).

Discussion

OPTIMAL ATRIOVENTRICULAR INTERVAL

The benefits of atrioventricular sequential pacing in.

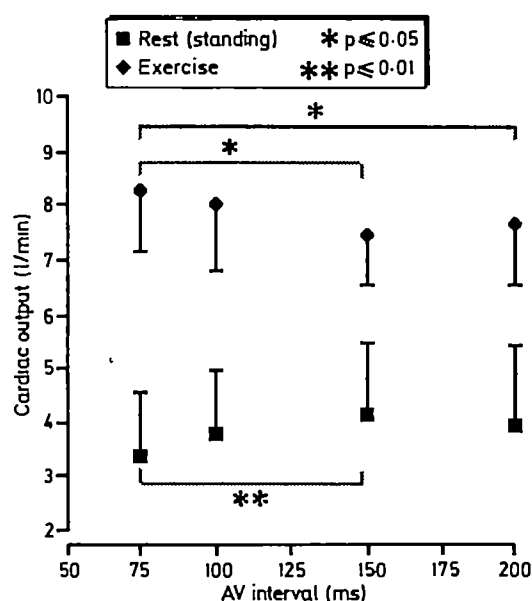


Fig 3 Mean (SD) increase in cardiac output on exercise showing an average 110% increase in cardiac output at all four atrioventricular intervals compared with values at rest (standing). The increase in cardiac output (from 3.4 (1.0) l/min to 8.1 (3.1) l/min) was greatest with a short atrioventricular delay (75 ms).

patients with complete heart block have been shown by invasive,³⁸ Doppler^{19,20} and radionuclide^{9,10,21} methods. During atrioventricular sequential pacing cardiac output was significantly affected by changes in atrioventricular interval. In our patients, all of whom had normal left ventricular function, an atrioventricular interval of 150 ms at rest was associated with maximum cardiac output. In previous studies, however, the optimal atrioventricular delay at rest varied between 150 ms and 200 ms.⁸⁻¹² This variability may be because the results for patients with normal and abnormal left ventricular function were grouped together. Videen *et al* used radionuclide ventriculography to show that patients with low ejection fraction functioned better at a longer atrioventricular interval,²¹ whereas a shorter atrioventricular interval gave the highest cardiac output in patients with heart block complicating acute myocardial infarction. Leinbach *et al* and Chamberlain *et al* found that the optimal atrioventricular interval was 150 ms in patients with chronic complete heart block and 100 ms or less in patients with heart block complicating acute myocardial infarction.^{9,22} Hartzler *et al* also showed that a comparatively short atrioventricular interval was associated with a higher cardiac output during the

period immediately after operation in patients in whom heart block developed at operation.²³ Thus in patients with normal left ventricular function who are at rest an atrioventricular delay of around 150 ms is optimal. In patients with impaired left ventricular function a longer delay is optimal. In situations of acute stress like myocardial infarction and post-operative states, where the heart rate is expected to be faster, a relatively short atrioventricular delay was found to be optimal.

Although others showed that an atrioventricular delay of 150–200 ms was associated with maximal cardiac output at rest, we found that this delay is not optimal during exercise. Our results confirm the observations of Leman and Kartz who found that on exercise a shorter atrioventricular interval was associated with a larger stroke volume.¹⁰ In their study, however, left ventricular function was assessed only at atrioventricular intervals of 100 and 150 ms and cardiac output was not measured. The results of our study accord with the observation that exercise and its catecholamine response is associated with a shortening of the PR interval in subjects with normal atrioventricular conduction.²⁴

EFFECT OF ATRIOVENTRICULAR INTERVAL ON CARDIAC EVENTS

The benefits of atrioventricular sequential pacing are related to the timing of atrial contraction, which if appropriate leads to an increment in ventricular filling and thereby to a ventricular contractile force (according to Starling's law).²⁵ To contribute most to left ventricular filling, atrial contraction must coincide with late diastole so as to cause maximum filling of the ventricle before onset of systole. In a recent study that used Doppler assessment of mitral flow, Iwase *et al* reported maximal left ventricular filling with an atrioventricular interval of 150 ms in patients at rest.⁵ When they measured mitral flows during early and late diastole they found that decreased left ventricular filling with a suboptimal atrioventricular interval was mainly caused by a decreased atrial (late diastolic) component. Both very short and long atrioventricular intervals reduced left ventricular filling.

With a physiological atrioventricular delay, atrial systole causes a surge of blood into the ventricle at the end of diastole. When the atrium relaxes, inertia causes this blood to continue flowing into the ventricle, producing a region of reduced pressure between the valve cusps, which are therefore pulled into apposition (the so called atrioventricular theory of valve closure).^{26,27} If the atrial contraction is late in diastole (as with a short atrioventricular interval), ventricular systole starts when the atrioventricular valves are still wide open and this leads to mild mitral

or tricuspid regurgitation.²⁸ Furthermore, because ventricular systole starts before atrial emptying is complete the atrial contribution to left ventricular volume is less.⁷ Thus the cardiac output would be expected to decrease.

An atrioventricular interval that is longer than the physiological atrioventricular delay also leads to a decrease in left ventricular performance. Dean, as early as 1916, in isolated heart preparations, showed that longer intervals between atrial and ventricular systole (> 270 ms) allowed the atrioventricular valves to move into apposition and separate again before ventricular contraction started.²⁷ Subsequent studies have shown that an inappropriately long atrioventricular delay is associated with some mitral regurgitation at the onset of systole.^{29,30} Premature atrial systole also reduces the time available for atrial filling from the pulmonary veins; thus it would be less effective than atrial systole in end diastole, when atrial filling would be maximum. Furthermore, atrial systole too early in diastole leads to premature closure of the atrioventricular valves thereby shortening the duration of left ventricular filling.⁶ Studies by Iwase *et al* did show a decreased left ventricular filling volume with long atrioventricular intervals.³

A decrease in PR interval with physiological exercise is well known. This decrease is caused by an improvement in nodal conduction under the effect of sympathetic stimulation and the decrease in vagal tone. In healthy subjects Daubert *et al* showed a linear shortening of the atrioventricular interval during exercise with an increase in heart rate.²⁴ An increase in heart rate produces a disproportionate shortening of diastole compared with systole. If the atrioventricular interval were to remain constant, atrial systole would occur relatively early in diastole—a situation similar to that seen with unphysiologically long atrioventricular intervals at rest.

PROBLEMS ASSOCIATED WITH UNIFORM PROGRAMMING OF ATRIOVENTRICULAR INTERVAL

The major difficulty in programming the atrioventricular interval in patients with complete heart block and atrioventricular sequential pacemakers is the difference in the atrioventricular delay between atrioventricular sequential pacing and ventricular pacing with atrial tracking. In the case of atrioventricular pacing the atrioventricular interval begins with a paced event while with atrial tracking the atrioventricular interval begins with a sensed atrial event. Because there is a delay of 35–40 ms before atrial sensing, the mechanical atrioventricular delay is relatively longer despite a similar program-

med atrioventricular interval.^{6,31} This makes uniform programming of the atrioventricular interval during atrial and ventricular pacing and atrial tracking difficult. Most of the present generation of dual chamber pacemakers do not distinguish between the paced and sensed atrial activity. In five of our nine patients there was tracking at the atrium at rest. This is an expected problem because of the inherent variation in sinus rate at rest from one patient to another. In previous studies, including ours, where the basic pacing rates at rest have been programmed up to 80 or 90 beats/minute so that atrioventricular pacing is established, an atrioventricular interval of 150–200 ms has still been found to be optimal.^{11,12,18} However, during exercise in all our patients there was tracking of the atrium. This means that the relative changes in cardiac output on exercise are more relevant and indicate the benefit of a relatively short atrioventricular delay on exercise.

CLINICAL IMPLICATIONS

In patients with complete heart block and atrioventricular sequential pacemakers, rate modulation of the atrioventricular delay may improve cardiac haemodynamic function. The degree of exertion used in our study was quite mild but it is likely that the haemodynamic advantage of a shorter atrioventricular interval would also be seen with moderate to severe exertion. Further studies are needed to assess the effect on the exercise capacity of rate modulation of the atrioventricular interval.

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Determination of the ratio of pulmonary blood flow to systemic blood flow by derivation of amplitude weighted mean velocity from continuous wave Doppler spectra

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SUMMARY Conventional Doppler echocardiographic techniques for the estimation of blood flow ratios depend on the precise measurement of the diameters of the aorta and the pulmonary artery and the mean blood flow velocities in these vessels. A simpler and quicker method is described, based on the calculation of the systolic time integrals of the amplitude weighted mean velocities from continuous wave Doppler spectra within the great arteries. In 30 controls the mean (2 SD) ratio of pulmonary to systemic blood flow averaged 0.952 (0.085). The results of the new technique showed a good agreement with those of quantitative dye dilution and oximetry in 16 patients with intracardiac left to right shunts.

Current Doppler ultrasound techniques to assess flow rates are based on the Doppler angle, the cross section of the vessel, and the cross sectional mean velocity.¹ Measurement of the vessel diameter, especially that of the pulmonary artery, is critical. Furthermore, the velocity profile within the cross section of the great arteries is usually not uniform and may show variable degrees of skewness, which affect measurement of the mean velocity. So the clinical application of these time consuming techniques is limited.

We report a new approach based upon the calculation of the systolic time integral of the amplitude weighted mean velocity from continuous wave Doppler spectra. We used this new technique to measure the ratio ($Q_p:Q_s$) of pulmonary to systemic blood flow in 30 controls and 16 patients with intracardiac left to right shunts.

Patients and methods

BASIC PRINCIPLE

In contrast with conventional Doppler methods for assessing flow rates from cross sectional vessel area and mean velocity within the vessel, the approach we used is based on the principle that the backscattered power of the Doppler signal (square of the amplitude) recorded at any frequency is a measure of the number of erythrocytes moving at the corresponding velocity within the ultrasonic beam.² Brody who examined the basic difference between the amplitude and power of the backscatter concluded that in a model in which the erythrocytes are assumed to be randomly distributed the backscattered power is proportional to the number of erythrocytes.² However, if the erythrocytes were spaced regularly within the bloodstream the amplitude would be proportional to the number of erythrocytes.

Spectral analysis of the Doppler shifts, which is commonly available on commercial Doppler instruments, provides a graphic display of all blood flow velocities as a function of time. The sum of the individual velocities multiplied by their respective signal power is called the power weighted mean

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velocity (PWMV), which is proportional to the instantaneous blood flow rate³:

$$Q \sim \text{PWMV} = \int_{f_0}^{f_s} P(f) f df,$$

Q = flow rate; $P(f)$ = power of the spectral density; f = Doppler shift; df = differential of f ; f_0 = cut-off frequency of the wall filter; f_s = spectral range.

Hence, the time integral of the power weighted mean velocity is proportional to the blood flow rate per unit time.

EQUIPMENT

We used a real time phased array sector scanner (Hewlett Packard HP 77020) for cross sectional echograms and continuous wave Doppler signals. We also used additional software which permitted the calculation and simultaneous display of the amplitude weighted mean velocity. The duplex transducer contained a 2.5 MHz crystal set for imaging and a 1.9 MHz crystal set for continuous wave Doppler. The beam of the continuous wave was about 5 mm wide 3 cm from the transducer and 13 mm wide 10 cm from the transducer.

MODEL EXPERIMENT

We used a roller pump to pump blood at known flow rates through a plastic tube (20 mm in diameter) in a waterbath. Because the stroke volume of a roller pump is constant the flow rates were varied by changing the pump frequency between 80 and 170 beats per minute to achieve flow rates of 1.5, 2.0, 2.5, 3.0, 3.5, and 4.0 litres per minute. The tube was then insonated with the equipment described above. Because the Doppler angle was not determined this examination gave only relative values for stroke volumes. The haematocrit was constant during measurements. The Doppler spectra were recorded on video tape, digitised off line, and edited into a 1024 × 1024 × 8 bit video display memory. Data were analysed further by an IBM-AT personal computer. At each flow rate the time integrals of both the amplitude weighted and power weighted mean velocities were calculated and averaged over four beats.

RECORDINGS

Flow rates were measured at identical amplification in the pulmonary artery from a left parasternal approach and in the aorta through the apical window. The continuous wave Doppler beam superimposed on the sector image was always positioned along the axis of flow at an angle of zero by adjusting the transducer to get the highest Doppler shifts in the spectrum. The continuous wave spectrum, the amplitude weighted mean velocity, and the electro-

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cardiogram were recorded simultaneously on a Panasonic 6200 VHS video recorder. The time integral of the amplitude weighted mean velocity curve over individual cardiac cycles was measured by planimetry by a track ball system. For further calculations and comparisons we took the mean of the amplitude weighted mean velocity stroke integrals of the four beats with the highest amplitudes.

STUDY GROUP AND EVALUATION OF THE METHOD
Pulmonary (Q_p) and aortic (Q_a) flow rates were measured by Doppler echocardiography in 30 controls aged 7 to 40 years and in 16 patients aged between one and 35 years of age with intracardiac left to right shunts. Ten of the 16 patients presented with an atrial septal defect and six with a ventricular septal defect. In three patients (two with atrial and one with ventricular septal defect) measurements were performed before and after surgical repair. In all 16 patients the $Q_p:Q_a$ ratios determined by the Doppler technique were compared with the values derived from oximetric and dye dilution measurements obtained on the same day. In the absence of intracardiac shunting, $Q_p:Q_a$ is usually about 0.98.⁴ This ratio reflects the extra systemic blood flow supplied by the bronchial arteries. So the comparison of Q_p and Q_a in controls was a direct independent evaluation of the method.

STATISTICAL ANALYSIS

We assessed the extent of the agreement between the new method and oximetry and dye dilution by the method of Bland and Altman.^{5,6}

Results

MODEL EXPERIMENT

In the model experiment the relative stroke volumes calculated from the time integrals of the amplitude weighted mean velocity varied by -10 to +12% compared with the mean value of the stroke volume delivered by the roller pump. The time integrals of the power weighted mean velocity varied by -25 to +22%. The power weighted data were derived by simply squaring the amplitude values of the Doppler spectrum before any further calculation. Both the amplitude weighted and power weighted data gave consistently valid results over the entire range of the tested pump frequencies.

Because we found that the amplitude weighted mean velocity was as good as if not better than power weighted mean velocity in the assessment of relative stroke volumes, we used it for all subsequent clinical assessments of blood flow ratios. Amplitude weighted mean velocity was available on the Doppler machine we used.

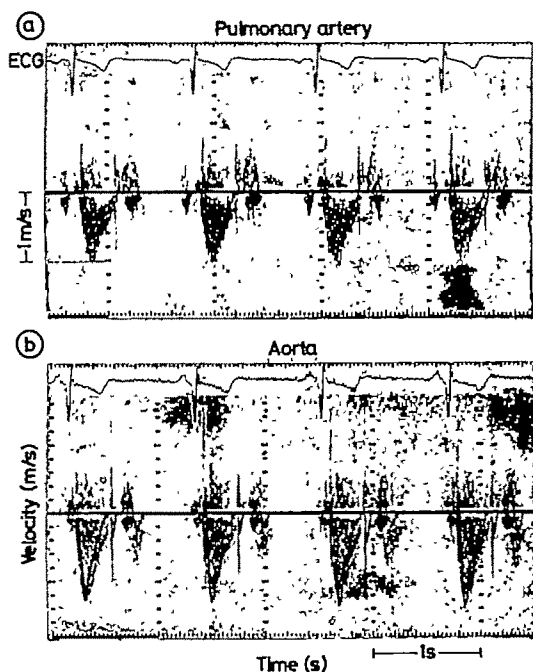


Fig 1 Doppler spectra and amplitude weighted mean velocities in a control. (a) Doppler spectra of the pulmonary artery from a left parasternal approach. The wave (solid line) is superimposed on the continuous wave spectrum. (b) Doppler spectra of the aorta from the apical window. The units for the amplitude weighted mean velocity are arbitrary. Paper speed 50 mm/s. ECG, electrocardiogram.

CLINICAL EVALUATION OF THE METHOD

In all 46 individuals we obtained adequate Doppler signals from both arteries. Figure 1 shows an example of a Doppler recording from the pulmonary artery and the aorta.

CONTROLS

In the 30 controls $Q_p:Q_s$ calculated from the average values amplitude weighted mean velocity in both arteries ranged from 0.86 to 1.04 (mean (2SD) 0.95 (0.016)) (fig 2).

PATIENTS WITH INTRACARDIAC LEFT TO RIGHT SHUNTS

In the 16 patients with left to right shunts caused by atrial or ventricular septal defects the values of $Q_p:Q_s$ estimated from Doppler amplitude weighted mean velocity correlated well with the values obtained by quantitative dye dilution curves or oximetry. Figure 3 plots the difference between the two methods versus the average of the two methods. Because the spread of the values increased with increasing values a log transformation was used.^{5,6} An additional scale on fig 3 shows $Q_p:Q_s$ measured by Doppler divided by

the value measured by dye dilution or oximetry. As the value of $Q_p:Q_s$ increases so does the scatter of the differences. None the less, for differences between 0 and 0.9—that is $Q_p:Q_s$ between 1.0 and 2.5 or shunts between 0 and 60%—scatter is considerably less than in the range above 2.5. So the increased scatter does not seriously affect values that are of clinical relevance.

Discussion

Recent developments in quantitative Doppler echocardiography have focused on the assessment of flow rate. It has been convincingly shown that both cardiac output and $Q_p:Q_s$ can be estimated from the Doppler flow velocity time integral and the cross sectional area of the bloodstream measured in the ascending aorta, the pulmonary artery, or the left ventricular inflow tract.¹ Nevertheless, the usefulness of these methods for routine clinical assessment is limited. Accurate determination of the mean blood flow velocity, and the adequate visualisation and measurement of the corresponding vessel diameter, especially that of the pulmonary artery, are major constraints on the assessment of the true flow rates. Moreover, such estimations are time consuming.

We found that estimation of $Q_p:Q_s$ from the time integral of the amplitude weighted mean velocity was valid. This new method is independent of the velocity profile within the vessels and does not need the measurement of the cross section of vessels.

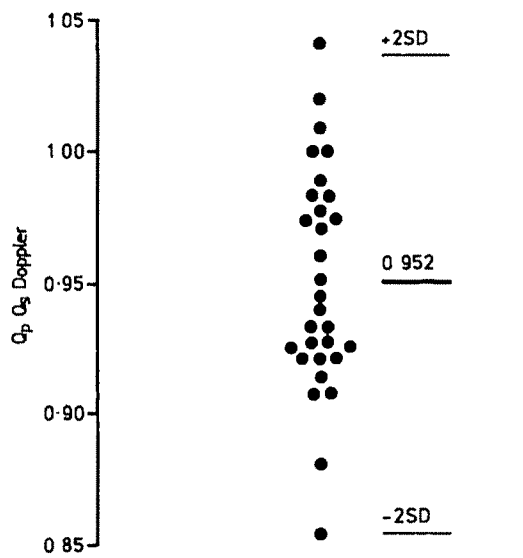


Fig 2 $Q_p:Q_s$ calculated from the time integrated Doppler amplitude weighted mean velocity in 30 controls. Except for three individuals Q_p was always smaller than Q_s .

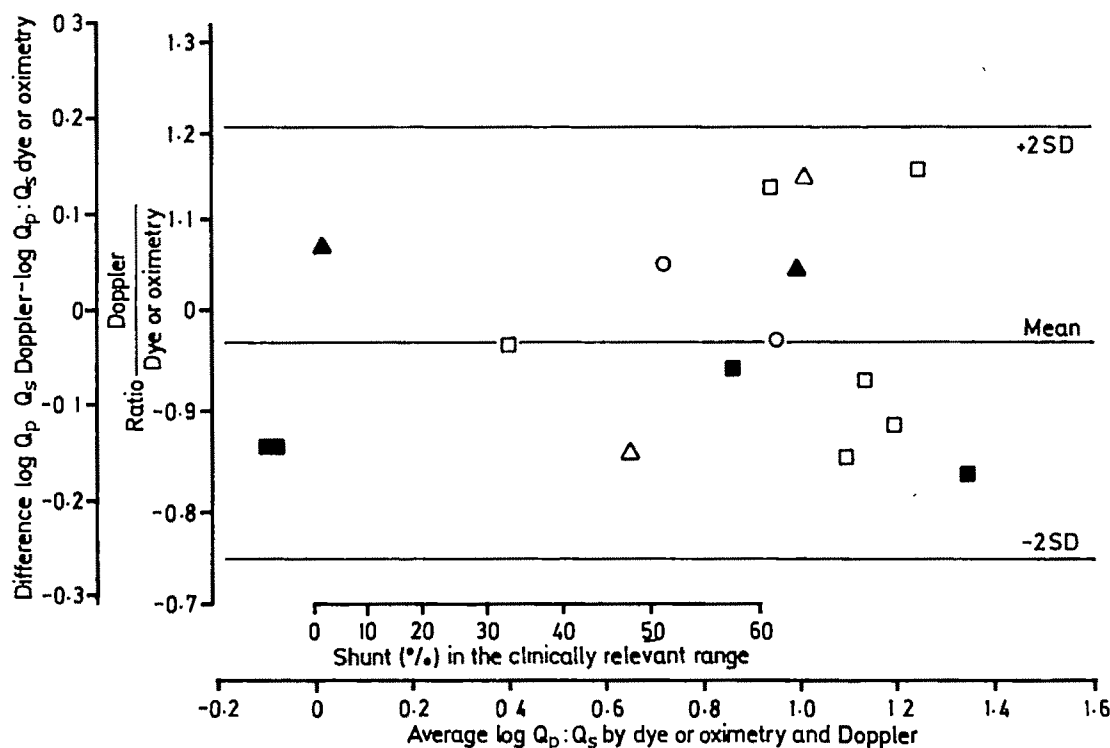


Fig 3 Difference between the ratio of blood flow in the pulmonary artery and aorta ($Q_p:Q_s$) measured by the Doppler method and dye dilution (dye) or oximetry plotted against mean $Q_p:Q_s$ for the two methods.^{5,6} Data for difference and mean were log transformed, because the scatter increased as $Q_p:Q_s$ increased. The y axis shows the ratios of the two methods. The clinically relevant range of shunts (0–60%) is indicated. Scatter within this range is small. Data came from 16 patients with intracardiac left to right shunts caused by atrial (squares) or ventricular (triangles and circles) septal defect. In patients represented by squares and triangles the reference method was dye dilution and in those represented by circles the method was oximetry. Solid symbols show three patients who were studied before and after operation.

We tested the method in 30 individuals without intracardiac shunting. The mean value of $Q_p:Q_s$ (0.95) corresponded to what is regarded as a physiological value.⁴ The range was between 0.86 and 1.04, indicating that even normal individuals may show "shunts" of up to 4%.

We compared the results of the new Doppler method with those of the conventional techniques of dye dilution and the Fick procedure in 16 patients with intracardiac left to right shunts. Agreement between the techniques was good, confirming the validity of the method for estimating $Q_p:Q_s$.

Our preliminary experiments with a roller pump model established that the relative stroke volumes based on both amplitude weighted and power weighted mean velocity calculations were accurate over the range of pump frequencies tested. The amplitude weighted mean velocity had the advantage of being less affected by ultrasonic attenuation than the power weighted mean velocity. In clinical measurements

the decrease in sensitivity as the distance of the region of interest from the transducer increases might bias the results because the distances between the transducer and the aorta and between the transducer and the pulmonary artery can differ appreciably. According to Carstensen *et al*⁷ blood attenuates the ultrasonic power at 1.9 MHz by about 17% per centimetre depth range, whereas the amplitude—that is the square root of the power—is reduced by 9% per centimetre range.

The time integral of the amplitude weighted mean velocity is a function of all the sound scattering features within the beam—that is scatter originating from the blood moving within the right or left ventricular outflow tract and blood moving within the great arteries distal to the annulus. It may be that amplitude weighted mean velocity does not reflect the true pulmonary or systemic flow rates. However, because of the continuity equation, maximum velocities within the continuous wave spectrum

occur at the site of the aortic or the pulmonary artery annulus. This is the smallest cross sectional area that blood has to pass when it is being ejected into the great arteries—so blood velocities are highest at the annulus. Moreover, because velocity profiles at the annulus are comparatively flat, these velocities are not only the highest ones recorded but also produce the most highly scattered amplitudes and thus contribute most to the amplitude weighted mean velocity.

The ideal of a homogeneously illuminated ultrasonic field covering the entire annulus area at any instant of the cardiac cycle, which would be a most desirable feature in amplitude weighted mean velocity measurements, is not achieved with the continuous wave Doppler system we used. In fact, with the arrangement we used, the width of the continuous wave Doppler beam is often less than the diameter of the annulus of the pulmonary or aortic valve.

To reduce the underestimation of $Q_p:Q_s$ in massive right heart dilatation future systems should use wider continuous wave Doppler beams

The use of amplitude weighted mean velocity is limited to the investigation of laminar flow. Turbulence in stenotic areas falsely increases the backscattered amplitude because erythrocytes are separated from blood plasma under these conditions.^{8,9} Another important feature in the assessment of amplitude weighted mean velocity is the fact that the method provides only relative values and does not reflect true stroke volumes. Therefore its use is limited to the determination of blood flow volume ratios.

We believe that the method we describe to estimate blood flow volume ratios by calculation of the amplitude weighted mean velocities within the great

arteries is accurate and, because of its simplicity, well suited to clinical use. As well as being suitable for measuring left to right shunts it may well be useful for determining the severity of mitral and aortic regurgitation by comparing aortic blood flow with left ventricular inflow and aortic blood flow with pulmonary blood flow.

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Unemployment, socioenvironmental factors, and coronary heart disease in Scotland

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SUMMARY Scotland, which has one of the highest death rates in the world from coronary heart disease, also has considerable regional variation in mortality from this cause. The relation between standardised mortality ratios for coronary deaths (1979-83) for 56 local government districts and a range of socioeconomic factors from the 1981 Census as well as climatic factors and water hardness were investigated. Strong associations were seen with several measures of social disadvantage, the strongest being with percentage of male unemployment. A fitted multiple regression model with mortality from coronary heart disease in men found independent effects of two social variables (percentage male unemployment and percentage social class III-V) and one climatic factor (rainfall). The model explained much (73%) of the geographical variation in mortality from coronary heart disease, but part of the geographical pattern, in particular some of the east-west gradient in mortality, remained unexplained by it. Explanations for the geographical variation and the association with economic factors are currently being sought in terms of individual risk factors in a large screening study, the Scottish Heart Health Study.

Mortality from coronary heart disease in Great Britain is among the highest in the world.^{1,2} There are, however, considerable differences within Britain.^{3,4} Many investigations have focused on England and Wales,⁵⁻⁷ whereas Scotland, which has the greater problem, has been comparatively neglected, although a recent paper has described a complex and interesting geographical pattern of mortality from coronary heart disease.⁸

There has been much concern about socioeconomic differences in mortality since the Black report on Inequalities in Health⁹ and the more recent report from the Health Education Council.¹⁰ One factor of particular interest has been the effect of unemployment on health.^{11,12}

The potential of socioenvironmental factors for explaining regional variation in disease mortality was recognised many years ago. In particular, the decennial censuses in Britain provide a wealth of regional data on socioeconomic variables and there have been

regional studies based around the 1951,¹³ the 1961,^{14,15} and the 1971¹⁶ censuses. Many of the studies of regional variation, however, have merely sought to control for socioeconomic factors while investigating physical factors such as water hardness,¹⁴ climate,^{6,17,18} or air pollution.¹⁶

We report an investigation of the association between socioeconomic and environmental factors and coronary heart disease in Scotland.

Methods

GEOGRAPHICAL UNITS, MORTALITY, AND POPULATION DATA

Local government districts were chosen as the geographical unit because they divide Scotland into a convenient number (56) of relatively homogeneous units.⁸ Deaths from coronary heart disease diagnosed according to the International Classification of Diseases 410-414 (ninth revision) for the age group 35-64 years for the period 1979-83 were obtained from the annual reports of the Registrar General (Scotland).¹⁹ Standardised mortality ratios were calculated for each sex as described by Armitage²⁰ for five year age specific mortality and population data from the 1981 census.²¹ The standardised mortality ratios for each sex for the whole of Scotland are defined as 100.

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SOCIOECONOMIC DATA

The 1981 *Census Reports for Regions* provides data on socioeconomic variables organised in four categories: demographic characteristics; economic characteristics; housing and amenities; and household composition.²¹ To ensure adequate coverage of the types of variables several (at least four) were selected from each category. One further variable (percentage of households with no car), which could not be allocated to one of the categories, was also taken. The choice of variables was taken to include (where possible) those used by two previous major studies.^{4,15} The variables chosen are listed in the appendix.

CLIMATIC DATA

Rainfall (average annual in millimetres) and temperature (overall means for January, July, and the whole year) were based on 30 year averages and obtained from the Meteorological Office (Edinburgh). The largest town in each district was linked to the closest meteorological station (often in the town itself) and 46 stations were used. Latitude and longitude were also taken for the largest town in the district according to the values given in *The Times Atlas of the World*.²²

WATER HARDNESS

Data on total and permanent water hardness were obtained from the departments of water services of the Scottish regional councils as previously described.²³

STATISTICAL ANALYSIS

Simple correlations—Spearman's rank correlation coefficient was used because several variables were highly skewed by outlying observations.

Multiple regression model—A linear additive model was fitted by the optimum method described by Pocock *et al.*²⁴ To enable comparison of the importance of the effect of the independent variables in the model the standardised regression effects were estimated.²⁵

Results

A map of coronary heart disease mortality among men showed an interesting geographical distribution (fig 1). There is a wide range in standardised mortality ratios (from 61 to 136) with a clear tendency for mortality to be high in the west and low in the east. In west central Scotland there was a grouping of high standardised mortality ratios, including eight of the highest ten districts. Within this grouping, however, are two districts with very low standardised mortality ratios (values of 61 and 73). There is also a block of

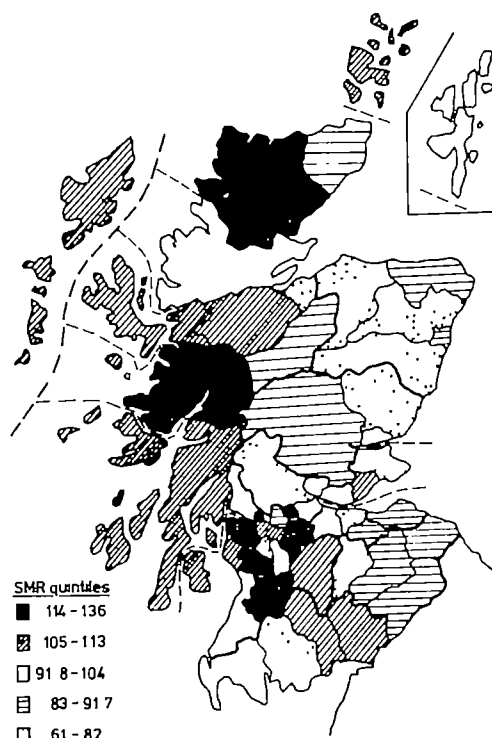


Fig 1 Standardised mortality ratios for coronary heart disease for men aged 35-64 years for the period 1979-83.

low mortality districts in the north east.

Mortality from coronary heart disease among women had a broadly similar pattern.⁸ Because these rates are based on much smaller numbers of deaths than for men (approximately one third of the number) they are potentially much more variable. Thus in the following analyses only the results for men are presented and those for women are alluded to.

The complex pattern of mortality raises the question of which factors are responsible for it, and in particular what is the role of socioeconomic factors. Table 1 shows the simple correlations between the standardised mortality ratios of male and female coronary heart disease and several socioenvironmental variables. The socioeconomic variables shown are those that had correlations with coronary heart disease that were significant at the 1% level. There were strong correlations with several variables which indicated low social class or social disadvantage. The other variables that correlated strongly with male mortality were longitude and rainfall. These last two associations are expected because all three variables show a pronounced east-west distribution. Latitude,

Table 1 Association between mortality from coronary heart disease in men and women and certain socioenvironmental variables

	Rank correlation*	
	Male SMR	Female SMR
Socioeconomic:		
Population density	(0.12)†	0.38
Percentage population change	-0.33	-0.41
Percentage married	-0.29	(-0.12)
Percentage < 16 years	0.29	(0.10)
Percentage not private household	-0.29	-0.42
Percentage rural	(-0.15)	-0.34
Percentage male unemployed	0.74	0.74
Percentage female unemployed	0.74	0.70
Percentage men economically active	(-0.13)	-0.30
Percentage in manufacturing	0.37	0.40
Percentage social class III-V	0.66	0.57
Percentage council house rented	0.55	0.65
Percentage owner occupied	-0.54	-0.63
Percentage > one person/room	0.61	0.54
Percentage > 3 dependent children	0.35	(0.07)
Percentage single parent	0.39	0.55
Percentage single pensioners	(0.12)	0.37
Percentage no car	0.55	0.61
Environmental:		
Longitude	0.58	0.36
Rainfall	0.41	(0.16)
Latitude	(-0.17)	-0.41
Temperature	(-0.02)	(0.18)
Total water hardness	(-0.26)	(-0.10)

SMR, standardised mortality ratio.

*Spearman's rank correlation coefficient.

†Coefficients not significant at the 1% level are shown in parentheses.

temperature, and water hardness were only weakly correlated with mortality from heart disease in men.

To examine the extent to which socioenvironmental variables could explain the variation in coronary heart disease within Scotland a multiple regression model was fitted. The model assumes that the variables have an additive effect; fitting a model assuming a multiplicative effect (by taking the logarithm of the standardised mortality ratio) resulted in a model containing the same independent variables.

Three variables (percentage male unemployment, percentage social class III-IV, and rainfall) were found to have a significant independent association with mortality from heart disease in men (table 2). Their relative importance can be assessed by comparing the standardised regression effects, which gives the percentage change in the dependent variable for an increase of one standard deviation in the independent variable with the other variables being fixed. These indicate that the two socioeconomic variables, particularly male unemployment, have the greater effects, with that of rainfall being slightly weaker. Overall the model explains 73% of the variance in mortality from coronary heart disease in men.

The important question to ask of the regression

Table 2 Regression model of mortality from coronary heart disease in men on the socioenvironmental factors

Variable	Standardised regression effect
Percentage male unemployment	7.549
Percentage social class III-V	6.934
Rainfall	5.771

Percentage of variance explained = 73%.

model is the extent to which it can explain the geographical distribution of coronary heart disease shown in fig 1. One way to do this is to obtain that part of heart disease mortality not explained by the model (the residuals) and to investigate the geographical pattern of this unexplained mortality. This technique is an extension of that suggested by Gardner.¹⁵

The map of the unexplained mortality (fig 2) shows that the cluster of districts with high mortality in the west has largely disappeared. Thus whereas eight of the ten highest standardised mortality ratios were in this cluster, only three districts now remain in the top ten. One feature of the original map that is preserved is the block of low mortality districts in the north east. The interpretation of this map is that while part

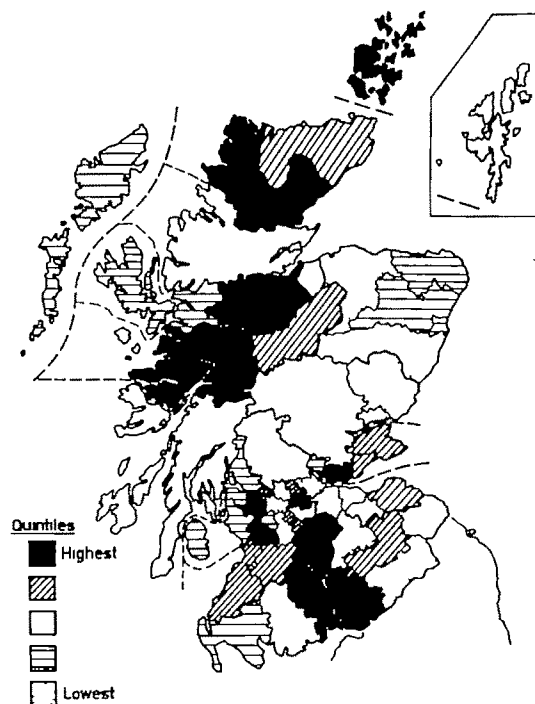


Fig 2 Quintiles of the residuals from the regression of mortality from coronary heart disease in men on the socioenvironmental variables.

of the geographical pattern can be explained by the fitted model a part remains that cannot.

Discussion

In Scotland, where mortality from coronary heart disease is one of the highest in the world,^{1,2} there is considerable geographical variation in this mortality. In contrast with Britain as a whole,³ there is not a south east to north west gradient but instead a pronounced east (low mortality) to west (high mortality) separation. Within a cluster of high mortality districts in the west, however, are two districts with very low mortality.

We found a strong association between this geographical variation in mortality and a range of measures of social disadvantage. Further, for male mortality a fitted regression model with two of these social factors (percentage male unemployment and percentage in social classes III-V) and one climatic one (rainfall) accounted for a large proportion (73%) of the variation in the geographical mortality.

Notable by their absence from the model and indeed for their lack of significant association with mortality from coronary heart disease are temperature and water hardness. The observation that within England and Wales there was an association between cardiovascular mortality and water hardness dates back to the early 1960s.¹³ In his review of the subsequent studies, including two of trends in mortality after changes in hardness of drinking water, Shaper²⁶ concluded that there was a weak causal relation between water hardness and cardiovascular mortality. The absence of a significant relation in Scotland, which we have reported previously,²³ does not exclude the possibility that water hardness may have a very small effect that could not be detected. However, the range of water hardness was that in which an effect, if it occurred, would have been detected.²⁶

An independent effect of climatic factors especially rainfall and temperature has been found in several studies.⁴⁻⁶ One group, however, has failed to find an association with temperature.⁷ The present study has found an effect of rainfall but not of temperature, so that the pattern in Scotland is not dissimilar to that in England and Wales. Several possible mechanisms have been suggested to account for the effect of climatic factors. These include body cooling, the enhanced spread of infection in winter months, and changes in physical activity (either inactivity or unaccustomed exercise).²⁶ At present the climatic effect remains an interesting unexplained observation.

The principal finding of this study was the importance of measures of social deprivation in explaining

the geographical variation in mortality from coronary heart disease in Scotland. There have been several studies relating cardiovascular disease or coronary heart disease to socioeconomic variables, usually just in England and Wales^{5-7,27} although one included some Scottish areas.⁴ Only the one including some of Scotland and that of Brenner²⁷ found that the social (or socioeconomic) factors had an independent association with mortality from cardiovascular disease; the others found weak or inconsistent effects. Part of the explanation for the lack of effect of social factors in previous studies could be that they dealt with earlier time periods. Mortality from heart disease changed from being higher in the non-manual occupations in the 1950s to being higher in the manual occupations in 1970-73.²⁸ This trend has continued, to produce an even larger manual-non-manual gradient in 1979-83²⁹—the period covered by the present study.

The finding of an increasing importance of social factors in coronary heart diseases raises questions about their meaning and the mechanism(s) by which they act. For example does the fact that male unemployment shows the strongest association with mortality mean that death among the unemployed is responsible for a large part of the geographical variation? This possibility is not supported by the range from 3.7% to 21.6% in unemployment rates. To produce the large range in coronary heart disease mortality ratios, from 61 to 136, the mortality rate among the unemployed, because they are such a small proportion of the whole population, would have to be many times that of those in employment. Although mortality may be higher among the unemployed^{11,12} this is not sufficient to contribute greatly to the observed geographical pattern.

It has been suggested that social factors⁴ may reflect a generally unhealthy lifestyle. This, however, begs the question of what are the "unhealthy lifestyle" features, and how do they translate into biological risk factors. Two studies^{30,31} which investigated this found that only part of the social class differences could be explained by the classic risk factors (smoking, serum cholesterol, blood pressure). Further, although two of these risk factors, smoking and raised blood pressure, followed the expected pattern, the third, serum cholesterol, was actually lower in the manual workers. The idea that there may be major unknown risk factors awaiting identification has been rejected by one group.³¹ But another group claimed that fibrinogen may be just such a new risk factor,³² so the matter is far from being settled.

Whatever the mechanism by which these social factors operate it is clear that an important part of the geographical variation in mortality from coronary heart disease remains unexplained by them. Thus we

found that although the cluster of high mortality districts in the west may be largely explained by the social factors, the area of low mortality in the north east is not. It is clear that routine data on mortality and censuses pose as many questions about socio-economic status, lifestyle, and coronary risk factors as they answer. Linked to this statistical exercise has been a large-scale survey of coronary risk factors and lifestyle in 22 of the Scottish districts of 12 000 men and women, called the Scottish Heart Health Study.³³ This study aims to investigate the factors underlying the geographical and social variation in mortality from coronary heart disease; the results are being analysed currently.

The Cardiovascular Epidemiology Unit is funded by the Scottish Home and Health Department.

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Appendix The socioeconomic categories and variables selected for initial analysis^a*Demographic*

- (1) Population density (persons per hectare)
- (2) Percentage net change in population between censuses (1971 minus 1981)
- (3) Percentage married adults^b
- (4) Percentage population less than 16 years
- (5) Percentage population not in private household^c
- (6) Percentage population in rural areas (localities of less than 1000 population)

Economic characteristics

- (7) Percentage men unemployed ages 16-64
- (8) Percentage women unemployed ages 16-59
- (9) Percentage men economically active ages 16-64^d
- (10) Percentage women economically active ages 16-59
- (11) Percentage men in manufacturing industry ages 16+
- (12) Percentage men aged 16-64 in private households in social classes III, IV, and V

Housing and amenities

- (13) Percentage households council rented
- (14) Percentage households owner occupied
- (15) Percentage households not in self-contained accommodation
- (16) Percentage households sharing or lacking a bath

Household composition

- (17) Percentage households with more than one person per room
- (18) Percentage households with three or more dependent children
- (19) Percentage children under 16 in households with lone adult
- (20) Percentage usually resident pensioners living alone

Other

- (21) Percentage households with no car

^aAll population data refer to usually resident persons.^bAdults are aged ≥ 16 .^cThose in hospital, hostels, defence establishments, prison.^dEconomically active includes those in employment and those seeking employment.

Clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy: association with left ventricular apical aneurysm

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SUMMARY Of 51 patients with hypertrophic cardiomyopathy who had episodes of ventricular tachycardia detected during ambulatory electrocardiographic monitoring only two had clinical sustained uniform ventricular tachycardia that required medical treatment because of worsening symptoms. In both patients the arrhythmia was associated with the uncommon finding of an apical aneurysm with angiographically normal coronary arteries.

Ventricular tachycardia was detected during ambulatory electrocardiographic monitoring in 20-30% of unselected adults with hypertrophic cardiomyopathy.^{1,2} The characteristics of these episodes was relatively homogeneous.³ The ventricular tachycardia was slow, non-sustained, and asymptomatic, but it was a marker of subsequent sudden death.¹⁻⁶ Sustained ventricular tachycardia is rare and clinical characterisation of such patients has not been reported. We present two of 51 consecutive patients with ventricular tachycardia in whom episodes were rapid, sustained, and symptomatic; both patients also had a left ventricular apical aneurysm.

Patients and methods

CASE 1

Hypertrophic cardiomyopathy without a left ventricular gradient was diagnosed in a symptom free 40 year old man who presented in 1972 with an abnormal electrocardiogram (fig 1a). Angiography showed an apical left ventricular aneurysm with normal coronary arteries (fig 2). Two years later he presented with rapid palpitation and hypotension. Sustained

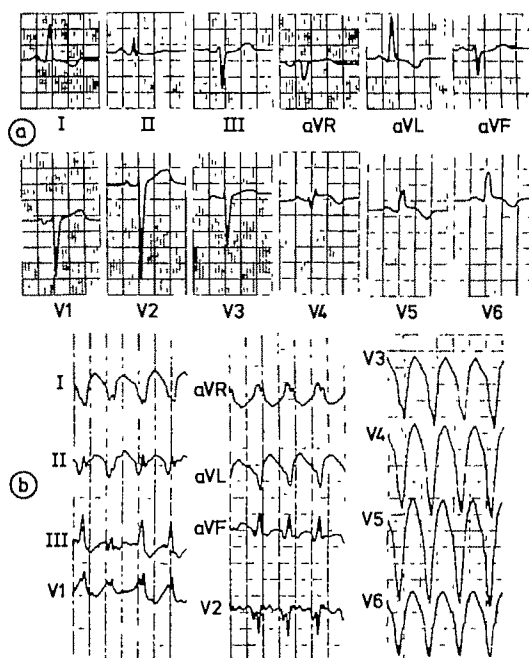


Fig 1 (a) Electrocardiogram from patient 1 showing sinus rhythm with poor R wave progression in the right precordial leads and ST segment elevation in leads V4-V6. (b) Clinical sustained uniform ventricular tachycardia with right bundle branch block configuration. The axis is $+160^\circ$ and the QRS width 160 ms. A fusion complex (beat 2) is shown in the first panel.

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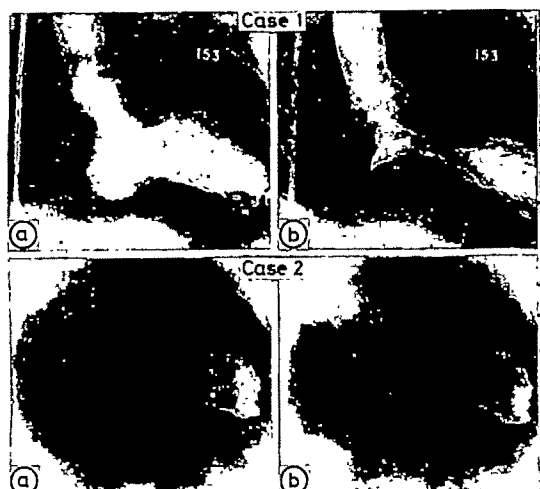


Fig 2 Diastolic (a) and end systolic frames (b) from left ventricular angiograms (right anterior oblique view) from case 1 (upper) and case 2 (lower). Both patients show systolic mid-cavity elimination with increased residual contrast and paradoxical wall motion at the apex.

uniform ventricular tachycardia (180 beats/minute) required DC cardioversion. During a four week stay in hospital repeated episodes of sustained ventricular tachycardia with a consistent configuration (fig 1b) were not controlled with lignocaine, quinidine, or procainamide. An electrophysiological study was performed off medication in 1975. Sustained ventricular tachycardia with the same configuration could be repeatedly induced from the lateral border of the aneurysm and reproducibly terminated by two ventricular extrastimuli. Between 1975 and 1981 drug regimens that included disopyramide (2 g/day) plus propranolol (120 mg/day) and quinidine Durules (400 mg/day) plus verapamil (120–240 mg/day) were associated with gastrointestinal and neurological side effects, while dose reductions were associated with recurrence of the arrhythmia. Ventricular arrhythmias did not develop during maximal exercise tests. However, even during asymptomatic periods, episodes of non-sustained ventricular tachycardia were shown during electrocardiographic monitoring. In 1981 all other medications were stopped and amiodarone was started. A daily dose of 400 mg was required to maintain a minimum effective plasma concentration of amiodarone and desethylamiodarone (1.6 and 1.3 mg/l respectively).⁶ For the past four years the patient has been symptom free without adverse effects or ventricular arrhythmia during electrocardiographic monitoring. Recent non-invasive evaluation confirmed the diagnosis and the abnormal anatomy. High gain, signal averaged electrocardiography performed by Simson's method⁷ with high-pass filtering at 25 Hz showed a prolonged

filtered QRS duration of 150 ms (normal < 120 ms), a prolonged duration of terminal filtered QRS below 40 μ V of 41 ms (normal < 40 ms), and a reduced root mean square voltage in the last 40 ms of 18.1 μ V (normal > 25 μ V). Cross sectional echocardiography showed asymmetric septal hypertrophy with maximum wall thickness of 2.2 cm in the septum and left ventricular free wall at papillary muscle level. There was hyperdynamic contraction at the base of the left ventricle with mid-cavity elimination and an apical aneurysm which was best visualised from the apical two chamber view. There were no echocardiographic or Doppler features of a gradient but colour Doppler showed evidence of mild mitral regurgitation. Phase analysis of technetium-99m radionuclide ventriculography showed that the apex was 180° out of phase with the body of the left ventricle.

CASE 2

A 56 year old Indian man with familial hypertrophic cardiomyopathy and a history of exertional chest pain and syncope was referred after a syncopal episode associated with palpitation during which sustained uniform ventricular tachycardia was documented. The tachycardia was at a rate of 190 beats/minute with right bundle branch block configuration, an axis of -120° , and a QRS width of 140 ms. Over a 40 year period he had experienced six other syncopal episodes that were not associated with chest pain or palpitation. Episodes of exertional chest pain began when he was 26, were often prolonged (1–2 hours), but were not associated with characteristic electrocardiographic changes of ischaemia or with increased plasma concentrations of myocardial enzymes. They were not consistently relieved by nitrates but treatment with verapamil was associated with fewer episodes (about one a month) than β blockers. An electrophysiological study was performed off medication in India. Single and double ventricular extrastimuli failed to induce sustained ventricular arrhythmias. Treatment with sotalol, verapamil, and verapamil plus procainamide failed to suppress episodes of non-sustained ventricular tachycardia during electrocardiographic monitoring.

Our investigations, which were performed after antiarrhythmic drugs were stopped, showed an abnormal electrocardiogram (fig 3a) and frequent ventricular extrasystoles (> 1000 daily) with daily episodes (1–5, median 3) of uniform non-sustained ventricular tachycardia at a rate of 160–180 beats/minute (fig 3b). Exercise testing was limited by fatigue and breathlessness at a maximal oxygen consumption of 26 ml/kg per minute and no arrhythmia or additional ST segment changes were seen. Cross sectional echocardiography showed asymmetric septal hypertrophy and a small left ventricular apical chamber that expanded during systole. The

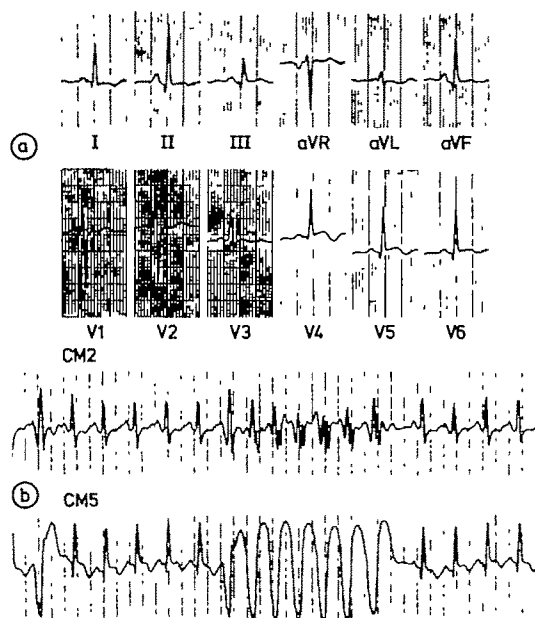


Fig 3 (a) Electrocardiogram from case 2 showing sinus rhythm with a normal QRS axis and non-pathological Q waves in inferolateral leads. The pattern of ST segment abnormality and elevation in precordial leads V4-V6 is similar to that seen in case 1. (b) Continuous ambulatory electrocardiographic recording of an episode of non-sustained ventricular tachycardia that was similar in configuration to the sustained episode and to other non-sustained episodes.

wall was thickest (2.4 cm) in the anterior and posterior septum and the free wall at the level of the tip of the mitral valve; there was incomplete systolic anterior motion of the mitral valve. The papillary muscles were greatly hypertrophied with systolic mid-cavity elimination that was associated with a mosaic pattern of turbulent flow on colour Doppler. At cardiac catheterisation there was no resting left ventricular outflow tract or mid-cavity gradient and the left ventricular end diastolic pressure was 26 mm Hg. Left ventricular angiography (fig 2) showed an akinetic area at the apex with dynamic contraction at the base; the coronary arteries were angiographically normal, apart from a separate origin of the left circumflex and systolic compression of septal perforator arteries. Radionuclide ventriculography with technetium-99m showed mid-cavity elimination with an apical aneurysm that on phase analysis was 180° out of phase with the remainder of the left ventricle. During the past year the patient was symptom free on amiodarone 400 mg daily with plasma concentrations of amiodarone and desethyl-amiodarone of 1.4 and 1.1 mg/l respectively. During 24 hour electrocardiographic monitoring there was a maximum of 240 uniform ventricular extrasystoles and no ventricular tachycardia.

Discussion

Non-sustained ventricular tachycardia is common in adults with hypertrophic cardiomyopathy.¹² Though episodes are asymptomatic they are associated with subsequent sudden death and are a relatively sensitive and specific marker of the high risk patient.²⁻⁶ Clinical episodes of sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy are rare. To our knowledge only two such patients have been reported.⁸ In a review of published reports, six other patients were selected for electrophysiological study because of clinical ventricular tachycardia or ventricular fibrillation, but no haemodynamic, echocardiographic, or additional arrhythmia data were available.^{9,10} A patient with polymorphic ventricular tachycardia who died suddenly after a period of autonomic disturbance and ischaemia has recently been reported.¹¹

Both of our patients with sustained uniform ventricular tachycardia also had a left ventricular aneurysm with angiographically normal coronary arteries. The apical aneurysms were shown angiographically and confirmed by echocardiographic and radionuclide studies. We did not see this configuration in the 49 patients with non-sustained ventricular tachycardia or in over 200 patients with hypertrophic cardiomyopathy without ventricular tachycardia who were similarly evaluated. Apical aneurysm in hypertrophic cardiomyopathy has been reported but is rare and is usually associated with normal coronary arteries.¹²⁻¹⁴ A recent report suggested that the presence of mid-ventricular obstruction may predispose to wall motion abnormalities in the distal left ventricle.¹⁵ When our patients were first examined there was no evidence of a left ventricular gradient; however, mid-ventricular obstruction earlier in their course cannot be excluded. Alternatively the apical myocardial changes may have been caused by coronary artery spasm with myocardial infarction.¹⁴

The electrocardiograms in our patients showed diagnostic clues with precordial ST segment elevation in the absence of abnormal Q waves. This pattern was reported by Gordon *et al* in three patients with apical aneurysm.¹⁵ Similar electrocardiographic changes were not seen in a review of electrocardiograms from 100 consecutive patients with hypertrophic cardiomyopathy who did not have left ventricular aneurysm.¹⁶ We agree with Gordon's suggestion that these electrocardiographic features may be a marker of ventricular aneurysm.¹⁵ The patient in whom high gain, signal averaged electrocardiography was performed (case 1) had late potentials. The association between the presence of late potentials and a propensity to ventricular tachycardia, especially in patients with left ventricular aneurysm, has been well established,¹⁷ though the relevance of such a finding in patients with hypertrophic cardio-

myopathy has not yet been systematically investigated.

Sustained uniform ventricular tachycardia is also uncommon during programmed electrical stimulation studies for the evaluation of clinical arrhythmias or identification of high risk patients with hypertrophic cardiomyopathy.^{8-10,18-24} More commonly multiform ventricular tachycardia or ventricular fibrillation or both is induced. The clinical significance of these induced arrhythmias is controversial.^{8-10,19-24} Recent studies have emphasised that to enhance the specificity of the results less vigorous protocols should be used.^{8,20,24}

The prognostic significance of clinical sustained uniform ventricular tachycardia in hypertrophic cardiomyopathy, whether or not it is related to the presence of apical aneurysm, remains to be established. Both patients are symptom free and without recurrence of arrhythmia during long term treatment with amiodarone. Should it be necessary, surgical aneurysmectomy remains an option.

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Determination of left ventricular volumes by Simpson's rule in infants and children with congenital heart disease

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SUMMARY Regression equations were developed from left ventricular casts of known volumes to calculate left ventricular volumes from biplane cineangiography obtained in non-standard views. Volumes were calculated by Simpson's rule from casts of postmortem specimens from patients with congenital heart disease. The casts were divided into two groups: those that came from patients with abnormal right ventricular haemodynamic function (group 1, $n = 11$) and those that came from patients in which it was normal (group 2, $n = 9$). Biplane cinegrams were taken in conventional (anteroposterior/lateral, right anterior oblique/left anterior oblique) and non-conventional (long axis oblique, hepatoclavicular, and sitting up) projections. The true volume of each cast was determined from its weight and specific gravity. Correlations between measured and true volumes ($r = 0.96$ to 0.99) were excellent in all projections, although each projection overestimated the true volumes (slope = 0.72 to 0.94). The regression equations obtained from conventional views were significantly different from those from the non-conventional views; however, the regression slopes in group 1 were not different from those in group 2 in any view.

Regression equations obtained by Simpson's rule do not seem to be affected by the haemodynamic state of the right ventricle. Different regression equations are required to measure left ventricular volumes from non-conventional angiograms.

In angiographic measurement of the left ventricle the area-length method described by Dodge and colleagues has become popular.¹ This method was derived from the assumption that the left ventricular cavity could be represented as a three-dimensional ellipsoid of revolution. In complex congenital heart disease, however, the left ventricle is not usually elliptical and it is affected by right ventricular haemodynamic function. Data from our laboratory question whether the area-length method can be applied to the non-elliptical left ventricle.²

Simpson's rule seemed to be independent of the

shape of the ventricle when it was applied to determining the volume of irregularly shaped right ventricles.³ We have assessed the accuracy of applying Simpson's rule to the determination of the volume of the left ventricle in patients with congenital heart disease and have evaluated the results of measuring left ventricular volume from conventional (anteroposterior/lateral, standard $30^\circ/60^\circ$ right and left anterior oblique) and non-conventional (long axis oblique, hepatoclavicular, and sitting up) projections.

Patients and methods

We studied casts of the left ventricles of 20 hearts of children and infants who died of congenital heart disease. All clinical data and data on haemodynamic function were reviewed. There were four hearts with endocardial fibroelastosis; three with atrial septal defect; three with tetralogy of Fallot; two with complete transposition of great arteries with intact

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ventricular septum; two with coarctation of aorta; two with total anomalous pulmonary venous return; two with myocardial disease; one with ventricular septal defect; and one with congenital mitral stenosis with pulmonary hypertension. The casts were prepared as previously described.⁴ Briefly, the post-mortem specimens selected were fixed in formalin; those in which ventricular shape had obviously been shrunk by fixation were excluded. After the removal of blood clots from both ventricles, the mitral and tricuspid valves were oversewn and the walls were glued with a cyanoacrylate compound (910 Adhesive, Permabond International Division). A silicon rubber material (3110 RTV, Dow Corning) mixed with barium sulphate powder (EZEM Co) was injected simultaneously into both ventricles through the aortic and pulmonary valves. The injection into the ventricles was performed as slowly as possible and without exerting positive pressure so as to avoid displacing the ventricular septum. After the casts had hardened, the left and right ventricular walls and free walls were incised and the casts were carefully removed. The true volumes of left ventricular casts were determined by weight divided by the specific gravity of the silicon rubber (1.17 g/dl).

Casts were placed on a goniometer designed in our laboratory and positioned on the catheterisation table. The vertical and horizontal image intensifiers were fixed in anteroposterior and lateral positions respectively. The initial reference position for the cast was established by a line connecting the apex with the most distal part of mitral valve that formed a 35° angle with the vertical plane and a 35° angle with the horizontal plane. The casts were filmed in conventional (anteroposterior/lateral, standard right anterior oblique and left anterior oblique) and non-conventional (long axis oblique, hepatoclavicular, and sitting up) positions. The exact positions of long axis oblique, hepatoclavicular, and sitting up projections were determined as previously described.⁵ The films were projected on a screen and the images were traced on to paper. After each film a grid of 1 cm squares was filmed at the cast centre parallel to each image intensifier.

The volumes of the left ventricular casts were calculated by Simpson's rule, which assumes that the cross section of each slice is cylindrical and that the total volume is the sum of all cylinders.⁶ For this calculation we used an IBM PC computer with dedicated software supporting a graphics tablet (Trinity Computer Systems, Houston, Texas).

We used standard linear regression analysis to compare the calculated volumes with the true volumes. We investigated the influence of left ventricular shape on volume determination by dividing the casts into those from patients with

abnormal right ventricular haemodynamic function (group 1, $n = 11$; atrial septal defect, tetralogy of Fallot, complete transposition of great arteries with intact ventricular septum, total anomalous pulmonary venous return, and congenital mitral stenosis with pulmonary hypertension) and those with normal right ventricular haemodynamic function (group 2, $n = 9$; endocardial fibroelastosis, ventricular septal defect, coarctation of aorta, and myocardial disease). We used analysis of covariance for between group comparisons of regression equations obtained from the five projections.

Results

The true volumes of the left ventricular casts ranged from 1 to 49 ml (mean (SD) 14 (13) ml) and those of the right ventricular casts from 2 to 34 ml (16 (10) ml). The ratio of the true volumes of the left and right ventricles was larger in group 2 than in group 1 (1.4 (0.6) v 0.7 (0.4), $p < 0.01$). These preliminary results suggested that the two groups could be separated on the basis of the haemodynamic function of the right ventricle. The shape of the left ventricular casts

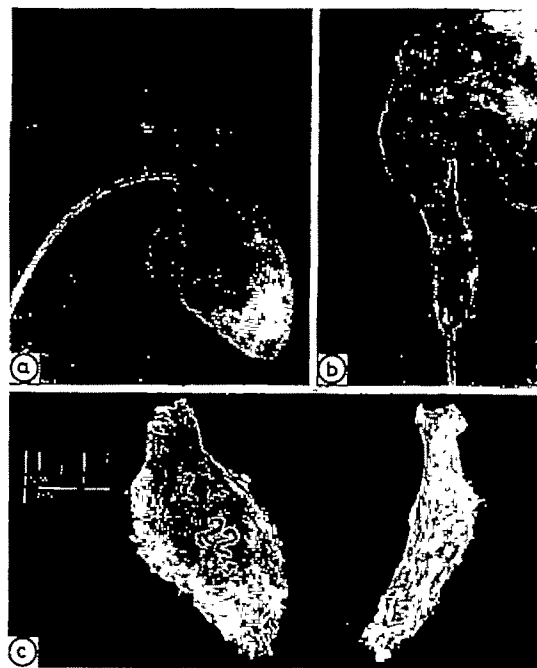


Figure The shape of the left ventricle shown by left ventriculography in one patient (a and b) and (c) a cast from another patient. Left ventriculography was performed in a patient with complete transposition of great arteries with intact ventricular septum and the cast was made from a postmortem specimen from a patient with complete transposition of great arteries with intact ventricular septum

Table 1 Regression equations obtained from all 20 casts

Projection	Regression equation	r value	Standard error of estimate
Anteroposterior/lateral	$y = 0.72x - 1.5$	0.96	3.6
Right/left anterior oblique	$y = 0.79x + 2.4$	0.98	2.6
Long axis oblique	$y = 0.84x - 2.4$	0.98	2.6
Hepatoclavicular	$y = 0.86x - 1.0$	0.97	3.3
Sitting up	$y = 0.94x - 2.9$	0.97	3.3

x, calculated volume, y, true volume; r, correlation coefficient.
Anteroposterior lateral v long axis oblique, hepatoclavicular, and sitting up projections, $p < 0.025$
Right/left anterior oblique v hepatoclavicular and sitting up projections, $p < 0.05$

closely resembled that of the left ventricle seen on the ventriculograms in the same projections (figure). Table 1 shows the results of the volume calculation in all projections. Regression analysis obtained from the 20 casts yielded excellent correlation coefficients ranging from 0.96 to 0.99 with small standard errors of estimate (2.1 to 3.6 ml). There were no differences in the slopes of the regression equations between the anteroposterior/lateral and right/left anterior oblique, or among the non-conventional axial views by analysis of covariance (table 1). However, the regression equations between anteroposterior/lateral and the non-conventional views, and right/left anterior oblique and two of the axial views (hepatoclavicular and sitting up) were significantly different ($p < 0.05$).

Comparison of the regression equations between group 1 and 2 showed no significant differences of slopes or intercepts in the five projections.

Discussion

Angiographic measurement of ventricular volume requires the use of regression equations to obtain corrected volumes. Regression equations have been obtained by comparing the known volumes of casts made from postmortem specimens and the volumes

Table 2 Comparison between groups 1 and 2 of regression equations

Projection	Regression equation	r value	Standard error of estimate
Anteroposterior/lateral	(1) $y = 0.54x + 0.4$	0.94	1.9
	(2) $y = 0.72x - 0.9$	0.96	4.9
Right/left anterior oblique	(1) $y = 0.70x - 1.7$	0.95	1.6
	(2) $y = 0.77x - 1.6$	0.98	3.5
Long axis oblique	(1) $y = 0.64x - 0.3$	0.91	2.2
	(2) $y = 0.85x - 1.9$	0.99	2.6
Hepatoclavicular	(1) $y = 0.98x - 2.1$	0.93	2.0
	(2) $y = 0.86x - 0.8$	0.99	2.3
Sitting up	(1) $y = 0.69x - 0.5$	0.96	1.1
	(2) $y = 0.95x - 2.3$	0.97	4.4

None of the differences between groups 1 and 2 was significant.

calculated by the area-length or Simpson's rule methods. Previous investigations have shown excellent correlations (correlation coefficient > 0.90) between calculated and cast volumes.⁷⁻⁹ In congenital heart disease, however, the left ventricle sometimes assumes a prolate shape because of abnormal right ventricular haemodynamic function. This may affect the accuracy of the area-length method, which assumes that the left ventricular cavity may be represented as a three-dimensional ellipsoid of revolution.^{10,11} Simpson's rule is usually applied to volume determination of right ventricle because the morphology of this chamber is less complex.¹² In our study, regression equations for the five projections yielded excellent correlation coefficients (> 0.96) with small standard errors of estimate (< 3.6 ml).

Comparisons between the groups showed there were no statistical differences between regression equations for different projections. These results suggest that Simpson's rule was not affected when the shape of left ventricle was altered by abnormal right ventricular haemodynamic function. We have previously reported that volumes calculated by the area-length method overestimated the true volumes if the haemodynamic function of the right ventricle is abnormal.² The present study suggests that Simpson's rule is more accurate than the area-length method because it is less dependent on the geometry of the ventricle. It seems that the prolate shape of the left ventricle (banana shaped) in simple transposition of the great arteries affects the estimation of the minor axis by the length-area approach.

The regression equations for conventional and non-conventional projections were statistically different in our study. To our knowledge, there are few previous investigations of the use of Simpson's rule to determine left ventricular volume in these non-conventional projections^{13,14} and no reports of investigations of the hepatoclavicular and sitting up projections. Previous studies of casts made from anatomically normal hearts did not show any differences in the slopes of regression equation between conventional and long axis oblique views. This may be because earlier studies used casts of different types or sizes. Our investigation suggests that different regression equations should be used to assess the size of left ventricle by left ventriculography in non-conventional views.

We conclude that Simpson's rule should be applied to the determination of left ventricular volume in complex congenital heart disease because it is more independent of the shape of the left ventricle. Non-conventional views, however, require different regression equations to calculate left ventricular volumes.

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Balloon dilatation of the aortic valve for congenital aortic stenosis in childhood

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SUMMARY Balloon dilatation of the aortic valve was attempted in 34 consecutive children aged 16 months to 17 years (median 7 years), weight range 9-60 (median 22) kg. Previous surgical valvotomy had been performed in two patients (twice in one of them). The valve was not crossed in one patient. In the remaining 33 patients the pressure difference between the left ventricle and the ascending aorta during systole was reduced from 71 (30) to 28 (19) mm Hg. In 24 patients recatheterisation 2-19 (mean 9) months later showed gradients that were similar to those immediately after balloon dilatation (35 (20) v 31 (20) mm Hg). The two patients with the highest residual gradients immediately after balloon dilatation showed a spontaneous reduction in gradient at repeat catheterisation, whereas the patient who had twice had previous surgical valvotomy showed an increase in gradient from 37 to 99 mm Hg over nine months and required aortic root replacement. Balloon dilatation was repeated in two patients and this caused a further reduction in gradient. New aortic regurgitation occurred in nine (27%) patients (grade I, 8; grade II, 1) and aortic regurgitation was exacerbated (grade I to II) in two of the nine with pre-existing aortic regurgitation. External iliac artery avulsion occurred in one (3%) patient and two (6%) required intravenous streptokinase because the femoral artery became occluded. There were no other complications. Open valvotomy was performed in the child in whom the valve was not crossed, but no other child required aortic valve operation.

Balloon dilatation of the aortic valve gave reasonable short term palliation and was well tolerated. It is an alternative to surgical valvotomy for initial palliation of congenital aortic stenosis in many children.

Relief of obstruction in congenital stenosis of the aortic valve in childhood has usually been by open surgical valvotomy. This, however, is a palliative technique, and survivors are at risk of late death and infective endocarditis and may need reoperation.¹⁻³ Aortic valve replacement in childhood is inappropriate because the patient will continue to grow. Also bioprosthetic valves are subject to calcification, and patients with mechanical prostheses will need anticoagulation. So a less hazardous non-surgical palliative technique to relieve aortic stenosis would have major clinical advantages.

Our success with balloon dilatation for pulmonary

stenosis,⁴ together with early reports of successful balloon dilatation in both congenital^{5,6} and, later, acquired aortic valve stenosis,⁷ led us to extend the technique to a consecutive series of infants and children with congenital aortic stenosis. We have already reported our experience with balloon dilatation of the aortic valve in neonates and infants⁸—an age group with problems that differ from those of older children with aortic stenosis. Our results in the smallest and sickest neonates were disappointing and similar to those associated with valvotomy in these patients. In the present study we report our early experience with balloon dilatation of the aortic valve for congenital aortic stenosis in childhood.

Patients and methods

Balloon dilatation of the aortic valve was attempted in

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34 consecutive children with aortic stenosis up to March 1988 at The Hospital for Sick Children, London (21 patients since April 1986) and Freeman Hospital, Newcastle upon Tyne (13 patients since June 1985). Patients were aged from 16 months to 17 years (median 7 years) and weighed 9–60 (median 22) kg.

Indications for balloon dilatation of the aortic valve were clinical evidence of at least moderate stenosis,¹ together with a measured peak to peak systolic pressure difference at previous catheterisation or Doppler peak instantaneous gradient of > 50 mm Hg. Most were symptom free. Only one child had heart failure and only two of the remainder reported symptoms. Previous surgical valvotomy had been performed in two (6%) patients (on two occasions in one of them). Previous coarctation repair had been performed in four (13%) patients, with balloon dilatation of recoarctation in one. None had a residual coarctation gradient of > 10 mm Hg.

Cross sectional echocardiographic measurement of the diameter of the aortic root was performed at the level of attachment of the aortic valve cusps in the parasternal long axis plane. Cardiac catheterisation was performed by standard techniques. General anaesthesia was used in 31 (91%) patients and local anaesthesia and basal sedation in three (9%). The femoral artery was entered via percutaneous puncture. A catheter to monitor arterial pressure was placed in the ascending aorta via the contralateral femoral artery in 24 patients to allow simultaneous measurement of pressure in the left ventricle and ascending aorta. In the remainder the transvalvar aortic pressure difference was measured during systole by pull back from the left ventricle to the ascending aorta. These patients were usually those of smaller body weight and the procedure avoided a second arterial puncture. Heparin (100 units/kg) was given. Angiography of the ascending aorta was used to assess the grade of aortic regurgitation and also to confirm the diameter of the aortic valve. This was estimated from the known catheter dimension.

Aortic regurgitation was graded as follows: (I) "whiff" of regurgitated contrast without outlining of the left ventricular cavity; (II) left ventricular cavity outlined by contrast which was always of lower density than that in the ascending aorta; (III) left ventricular cavity outlined by contrast medium which was of equal density to that in the ascending aorta in more than three beats; (IV) equalisation of contrast density in the left ventricle and ascending aorta within three beats.

The left ventricle was entered retrogradely with an end hole catheter, usually over a guide wire. An exchange guide wire was introduced to the left ventricle via this catheter. The soft tip of the wire was

curled in the left ventricular cavity. The balloon catheter (Meditech, Surgimed, or Cook) was introduced directly over the wire without an arterial sheath. A catheter with an inflated balloon size at least 1 mm less than the measured aortic root diameter was selected. The balloon was usually 3 or 4 cm long, although we used longer balloons (5.5 or 8 cm) in large patients in the latter part of the study. The balloon was purged of air, positioned across the aortic valve, and then inflated 2–5 times by hand with dilute contrast medium, the aim being to abolish the "waist" in the partly inflated balloon. Two balloons, each of 15 mm diameter, were inflated simultaneously in one patient in whom the measured diameter of the aortic valve ring was 23 mm. The balloon catheter was then exchanged for the end hole catheter and the difference in pressure between the left ventricle and the ascending aorta was remeasured during systole. If this was > 40 mm Hg, and a larger balloon with an inflated diameter less than or equal to the measured diameter of the aortic valve was available, the procedure was repeated with the larger balloon. Finally, aortography was repeated in the same projection as the initial aortogram. Haemostasis was achieved by digital pressure.

Results

IMMEDIATE RESULTS

The aortic valve was crossed retrogradely in all but one patient, who was the first in the series. He underwent surgical valvotomy. In the remaining 33 patients, the mean peak to peak systolic pressure difference between the left ventricle and ascending aorta was 71 (30) mm Hg (mean (SD)) before and 28 (19) mm Hg ($p < 0.001$) immediately after balloon dilatation (fig 1). In 13 patients we used sequential inflation of two balloons; the second was larger than the first. Four other patients had persisting gradients of > 40 mm Hg after the use of a single balloon but the next balloon size available was considered too large to be used safely. In the only patient with heart failure the systolic pressure difference between the left ventricle and ascending aorta was reduced from 46 to 12 mm Hg, and this was associated with reductions in pulmonary artery systolic pressure and right atrial mean pressure from 70 to 48 and from 20 to 10 mm Hg respectively. There was no relation between age and the extent of gradient relief.

REPEAT CATHETERISATION

To date 24 patients have had repeat cardiac catheterisation 2–19, mean 9 (4) months after the initial procedure. These repeat studies were performed under general anaesthesia in eight patients and basal sedation in the remainder. The mean peak to peak

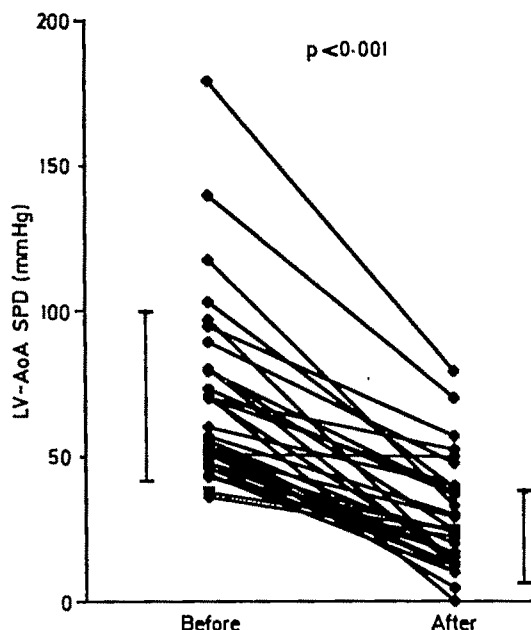


Fig 1 Systolic pressure difference between the left ventricle and ascending aorta before and immediately after balloon dilatation of the aortic valve. AoA, ascending aorta; LV, left ventricle; SPD, systolic pressure difference.

systolic pressure difference between the left ventricle and ascending aorta at restudy was 35 (20) mm Hg, compared with 31 (20) mm Hg immediately after balloon dilatation (fig 2). It is notable that the two patients with the highest residual gradient immediately after balloon dilatation had spontaneous reduction in gradient at repeat catheterisation (from 70 to 40 and from 79 to 30 mm Hg respectively). Repeat catheterisation was performed nine months after the initial procedure in each of these patients. The only patient who had a large increase in the systolic pressure difference between the left ventricle and ascending aorta at restudy was the patient who had twice undergone surgical valvotomy—via the trans-ventricular approach as a neonate and by open valvotomy on cardiopulmonary bypass at one year. There had been a large residual transvalvar gradient after each operation. He has subsequently undergone successful aortic root replacement. The systolic pressure difference between the left ventricle and ascending aorta had increased from 12 to 35 mm Hg in the patient who initially had heart failure and pulmonary hypertension. However, he has had major symptomatic improvement associated with a reduction in heart size on chest x ray and an improvement in the left ventricular shortening fraction on echocardiography.

Two patients with residual gradients of 50 and 59 mm Hg had repeat balloon dilatation 14 and 2 months after the initial procedure. We used a larger balloon than that used at the initial procedure in the first patient and two balloons inflated simultaneously in the second. In both cases the residual gradient was reduced (fig 2). There were only two other patients with residual systolic pressure differences between the left ventricle and ascending aorta of > 50 mm Hg. One, with a residual gradient of 65 mm Hg, is scheduled for repeat balloon dilatation. The other, with a residual gradient of 53 mm Hg, had a sub-valvar component to her left ventricular outflow tract obstruction and dilatation was not repeated.

COMPLICATIONS

All patients tolerated the procedure well. Aortic regurgitation was apparent before balloon dilatation in nine (27%) patients and not present in 24 (73%). After balloon dilatation (repeat balloon dilatation in two patients), aortic regurgitation had been induced in nine (27%) patients—grade I in eight (24%) and grade II in one (3%). Aortic regurgitation was

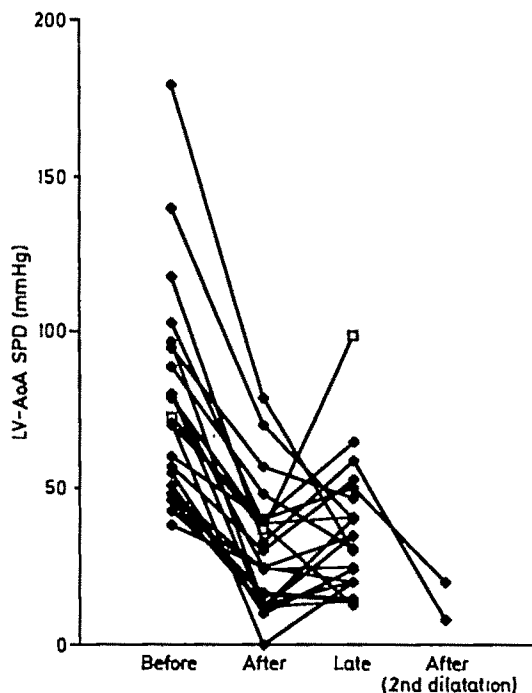


Fig 2 Systolic pressure difference between the left ventricle and ascending aorta before and after balloon dilatation of the aortic valve at later repeat catheterisation and after a second dilatation in two patients. The open symbol denotes the child with previous surgical valvotomy (see text). See fig 1 for abbreviations.

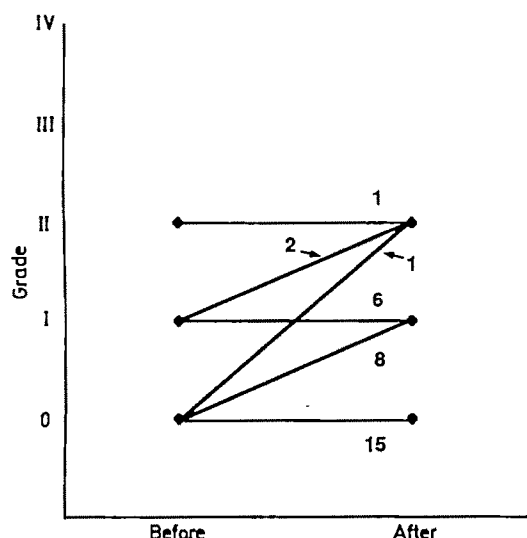


Fig 3 Angiographic grade of aortic regurgitation before and after balloon dilatation of the aortic valve. Numbers of patients are shown.

exacerbated, from grade I to II, in two (6%) patients. In most (22 patients, 67%) aortic regurgitation was not induced or was of similar severity before and after balloon dilatation (fig 3).

There was one major local arterial complication, when the external iliac artery was avulsed during withdrawal of a 15 mm, 9 French gauge balloon catheter in a child weighing 9.5 kg. This probably occurred because the 3.5 French gauge catheter introduced via the contralateral femoral artery to monitor pressure in the ascending aorta became entangled with the balloon catheter during withdrawal and was pulled down into the common iliac artery. This child underwent iliofemoral arterial reconstruction with an excellent (short term) result to date. This complication is avoidable, and our current practice is to withdraw the pressure monitoring catheter to the ipsilateral iliac artery before withdrawal of the balloon catheter. Two other patients required streptokinase when the leg pulses disappeared after the procedure. This was successful in one. In the other, pulses in the affected limb were palpable after streptokinase, but of reduced volume compared with the unaffected leg. No other local arterial complications were identified. Leg pulses remained palpable at the time of repeat catheterisation in all patients restudied to date.

FOLLOW UP

All patients remain well at follow up (time last seen) ranging from 1 to 24, mean (SD) 13 (7) months. The patient with heart failure and pulmonary hyperten-

sion before balloon dilatation is now symptom free at eight months follow up. A 14 year old boy with presyncope and dyspnoea is now symptom free after reduction of the systolic pressure difference between the left ventricle and ascending aorta of from 118 to 8 mm Hg. Syncope has not recurred in a 12 year old boy who had had unsuccessful surgical valvotomy. However, follow up is short (two months) and any benefit conferred by balloon dilatation in this case is doubtful (systolic pressure difference between the left ventricle and ascending aorta was reduced from 36 to 22 mm Hg). Several other children, with no reported symptoms initially, now have "more energy". No child has had a worsening of symptoms since balloon dilatation.

Discussion

Balloon dilatation of the aortic valve significantly reduced the transvalvar systolic pressure gradient both immediately after dilatation and at medium term repeat catheterisation in an unselected consecutive series of children with congenital aortic valve stenosis. The procedure was well tolerated, and was not difficult technically, in contrast with the technical difficulties experienced with very small infants.⁸ The child in whom the aortic valve could not be crossed at catheterisation was the first patient in the series, and he is the only child to have had surgical aortic valvotomy in either hospital during the study.

COMPLICATIONS

Aortic regurgitation was induced or exacerbated in 11 (33%) patients. Our estimates of the severity of aortic regurgitation are fairly crude, but only one patient had worsening of the angiographic severity by more than one grade; the systolic pressure difference between the left ventricle and ascending aorta was concomitantly reduced from 97 to 13 mm Hg. Selection of balloon size is important in minimising the severity of aortic regurgitation after the procedure. In an experimental study in lambs, use of balloons with an inflated diameter of 120–150% of the aortic root diameter resulted in tears in the aortic valve and tears or haemorrhage or both in the anterior mitral valve leaflet, ventricular septum, and ascending aortic wall.⁹ Oversized balloons used intra-operatively in infants caused similar damage.¹⁰

Local arterial complications were less common than those encountered after balloon dilatation of the aortic valve in infants, or after balloon dilatation for recoarctation of the aorta. Our only major local complication, which required iliofemoral arterial reconstructive surgery, was potentially avoidable. Although none of the children in this series lost leg pulses, in contrast with experience in infants,⁸ the use

of such large arterial catheters causes concern about the long term effect on limb growth. Introducing two balloons means slightly smaller catheters can be used, but both femoral arteries then become "at risk".¹¹

AORTIC VALVE AREA AND PRESSURE GRADIENTS

In theory any improvement could be confirmed either by estimating the aortic valve area or the pressure gradients. We did not attempt to measure the aortic valve area. An increase in aortic valve area after balloon dilatation has been calculated by others,⁹ using the original Gorlin formula for aortic valve area,¹² but in practice there are numerous problems in deriving accurate values. Firstly, the Gorlin formula¹² has never been validated in children. Secondly, it is difficult to measure cardiac output accurately.^{13,14} Thirdly, even if accurate values for mean transvalvar gradient and cardiac index are available, it may not be valid to use the Gorlin formula to compare changes in valve area before and after balloon dilatation. The original formula¹² produces an apparent increase in aortic valve area for the same valve as cardiac output increases. Finally, when aortic regurgitation is present, a measurement of effective systemic cardiac output will underestimate the transvalvar aortic flow. If aortic regurgitation of different severity is present in the situations in which aortic valve area is to be compared, comparison of the values obtained will be further confused.

Transvalvar aortic systolic pressure gradients, on the other hand, are more easily measured than aortic valve area, although pressure in the ascending aorta rather than more peripheral systemic arterial pressure should be compared with left ventricular pressure.¹³ Systolic pressure differences between left ventricle and ascending aorta are more familiar to physicians, and a peak gradient of > 60 mm Hg is advocated as a criterion for surgical valvotomy in congenital aortic stenosis.¹⁵ In the series of Hossack *et al*,¹ assessment of the severity of aortic stenosis correlated better with the systolic pressure difference between the left ventricle and aorta than with calculated aortic valve area index, suggesting that the latter derived value did not provide additional information on the severity of disease in these patients.

Children in our study had all catheter gradients measured either under general anaesthesia or basal sedation. All but the child with heart failure had echocardiographic left ventricular shortening fraction within the normal range before and after balloon dilatation. While a transient reduction in cardiac output immediately after balloon dilatation might have contributed to a transient decrease in the systolic pressure differences between the left ventricle and ascending aorta, the persistence of this

reduction at follow up catheterisation suggests a genuine improvement in the degree of obstruction.

COMPARISON WITH VALVOTOMY

Aortic valvotomy in childhood is a palliative procedure. Although initial operative mortality is low, and survival at 15 years may be as good as 80–87%,^{1–3} freedom from reoperation or a serious residual lesion over this period is as low as 14%² or 18%,¹ even in the most experienced surgical centres. Consequently, an alternative form of palliation which might delay, or occasionally avoid, the need for operation, while preserving the operative field, merits consideration. Our initial experience with balloon dilatation of the aortic valve suggests that the need for operation may be further delayed by repeat balloon dilatation in some patients.

The importance of aortic regurgitation induced or exacerbated by balloon dilatation is uncertain. After open valvotomy aortic regurgitation was an indication for surgery in 30–36% of patients who required reoperation.^{1–3} Thus provided that an oversized balloon is not used, the degree of aortic regurgitation induced by balloon aortic valvotomy may not be more than that induced by open surgical valvotomy.

With uncertainties about the natural history of congenital aortic stenosis in the era since the introduction of surgical intervention, automatic referral for open valvotomy of patients with congenital aortic stenosis and a peak systolic pressure gradient of > 60 mm Hg between the left ventricle and ascending aorta¹⁵ is unappealing because it only achieves palliation. Some patients with such gradients will survive for many years without evident progression of the severity of their disease.¹ There were only two sudden deaths among 174 unoperated patients out of a total series of 218 patients with congenital aortic stenosis followed for a mean period of nearly nine years.¹ Both patients had been lost to follow up for nine and four years when they died suddenly. However, it can be reasonably assumed that decompression of the left ventricle will have long term benefits for myocardial performance and balloon dilatation of the aortic valve may provide a low risk less traumatic alternative to open valvotomy. This initial form of palliation is suitable for many patients who are symptom free. Consequently, our criteria for balloon aortic valvotomy were more liberal than for open valvotomy. We do not suggest that there is an absolute indication for intervention in every patient fulfilling these criteria. Our experience with balloon aortic valvotomy after unsuccessful open valvotomy is limited to two patients, but suggests that balloon valvotomy may be ineffective in such patients.

COMPARISON WITH OTHER STUDIES

We obtained broadly the same reduction in gradient and low rate of serious complications as other centres.¹⁶⁻¹⁸ This accumulating experience suggests that the technique may be safely applied as a successful initial palliation over a wide age range in most children with congenital aortic stenosis.

CONCLUSION

Balloon dilatation of the aortic valve in a consecutive unselected series of children with congenital aortic stenosis provided reasonable relief of obstruction without inducing severe aortic regurgitation. Other complications have been infrequent. The technique has already had a major impact on our clinical practice. The encouraging short and medium term results indicate continuation of this policy of balloon dilatation for clinically significant aortic stenosis in children, but longer follow up is essential.

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Distinguishing between anomalous origin of the left coronary artery from the pulmonary trunk and dilated cardiomyopathy: role of echocardiographic measurement of the right coronary artery diameter

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SUMMARY Patients with anomalous origin of the left coronary artery from the pulmonary trunk usually have a large right coronary artery. This study examines the diagnostic value of measuring the diameter of the right coronary artery by echocardiography in distinguishing between this lesion and other causes of dilated cardiomyopathy. The diameter of the right coronary artery and the right coronary artery/aorta ratio were measured in the parasternal short axis view in 40 controls, 11 patients with dilated cardiomyopathy, and 10 with anomalous origin of the left coronary artery from the pulmonary trunk. In the controls, the diameter of the right coronary artery increased with age, but the right coronary artery/aorta ratio remained constant. In the control group the 95% upper limits of prediction for right coronary artery diameter were 1.6 mm for one month of age, 1.8 mm for three months, 2.0 mm for one year, 2.2 mm for two years, 2.4 mm for three years, 2.6 mm for four years, 2.7 mm for six years, 3.0 mm for eight years, and 3.2 mm for 10 years; and for right coronary/aorta ratios the limits were 0.17 for one month to one year, 0.18 for one to six years, 0.19 for six to 10 years, and 0.20 for more than 10 years. All patients with dilated cardiomyopathy had normal right coronary artery diameters and right coronary artery/aorta ratios (0.10-0.13). Those patients with anomalous origin of the left coronary artery from the pulmonary trunk had larger than normal right coronary artery diameter and a significant increase in the right coronary artery/aorta ratio (0.21-0.29).

The presence of an anomalous left coronary artery was likely if the diameter of the right coronary artery or the right coronary artery/aorta ratio was larger than the normal 95% limits of prediction.

Anomalous origin of the left coronary artery from the pulmonary trunk is one of the rare causes of dilated cardiomyopathy in infants and children.¹ Because an operation may give better results than medical treatment, early recognition and differentiation from other causes of dilated cardiomyopathy may be important in preventing the development of extensive myocardial damage.²⁻⁴ Recent advances in cross sectional echocardiography permit the diagnosis to be made non-invasively⁵; however, it may not always be possible to image the origin of the left coronary

artery from the pulmonary trunk.⁶ Similarly, confusion with the transverse sinus has given rise to false positives.⁷ On the other hand, the right coronary artery is usually dilated and tortuous in anomalous origin of the left coronary artery from the pulmonary trunk.^{8,9} This report assesses the role of measurement of diameter of the main right coronary artery by cross sectional echocardiography in distinguishing between this lesion and other forms of dilated cardiomyopathy.

Patients and methods

We studied 10 patients with anomalous origin of the left coronary artery from the pulmonary trunk (aged 3-79 months, median 7.5 months) (table 1), 11 with

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Table 1 Patients with anomalous origin of the left coronary artery from the pulmonary trunk

No	Age (month)	RCA (mm)	AO (mm)	RCA/AO
1	3	2.6	9.0	0.29
2	3	2.2	9.0	0.26
3	4	2.3	9.5	0.24
4	7	2.2	10.0	0.22
5	8	2.0	10.0	0.20
6	9	3.0	11.0	0.27
7	15	3.5	12.0	0.29
8	55	3.6	17.5	0.21
9	70	4.4	15.5	0.28
10	79	3.9	18.0	0.22

AO, diameter of the aortic root; RCA, diameter of the right coronary artery; RCA/AO, ratio of right coronary artery to aorta.

Table 2 Patients with dilated cardiomyopathy

No	Age (month)	RCA (mm)	AO (mm)	RCA/AO	Aetiology
1	2	0.9	9.0	0.10	EFE
2	3	1.1	9.0	0.12	EFE
3	4	1.1	9.5	0.12	EFE
4	6	1.1	10.0	0.11	EFE
5	6	1.2	10.0	0.12	EFE
6	7	1.2	10.0	0.12	EFE
7	7	1.1	10.0	0.11	EFE
8	13	1.2	12.0	0.10	EFE
9	44	1.7	13.0	0.13	ICM
10	54	1.6	14.0	0.11	ICM
11	113	1.9	17.0	0.11	ICM

AO, diameter of the aortic root; EFE, endocardial fibroelastosis; ICM, idiopathic cardiomyopathy; RCA, diameter of the right coronary artery; RCA/AO, ratio of right coronary artery to aorta.

dilated cardiomyopathy of another cause (aged 2–113 months, median 7 months) (table 2), and 40 controls (aged 1–123 months, median 29.5 months). The cause of the dilated cardiomyopathy was endocardial fibroelastosis in eight patients and idiopathic cardiomyopathy in three patients.

We reviewed videotapes recorded from a standard approach with a 7.5 MHz transducer. We used a parasternal short axis view at the level of the right coronary artery for all patients and controls. The vessel was measured between 0.5 and 1 cm from the ostium. This enabled the diameter to be assessed in

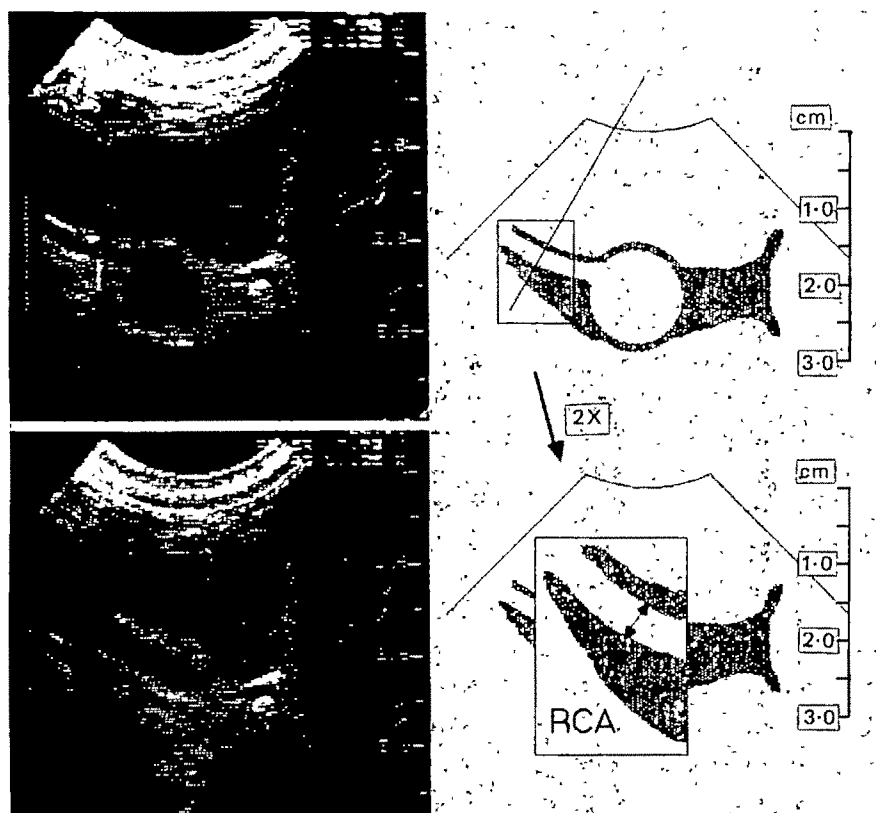


Fig 1 Echocardiographic method for measurement of right coronary artery (RCA) and aortic diameters. Measurement line is aligned with the axial beam. Right coronary artery is measured in a magnified image by PGS (Professional Graphic System, Symtec).

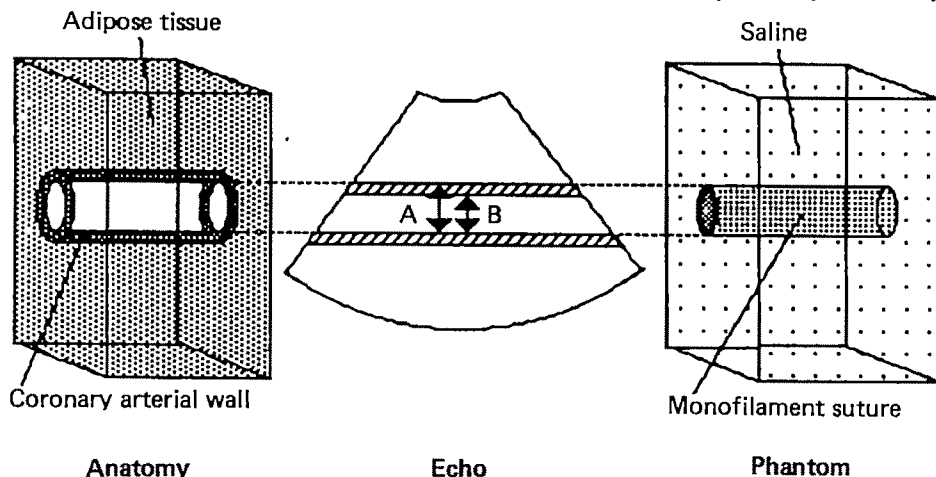


Fig 2 Custom phantom model for assessing the accuracy of the measurement of the coronary artery. A, leading edge method; B, internal measurement. See text for explanation.

the axial plane of the ultrasound beam. The distance between the transducer and right coronary artery varied from 1 cm to 3 cm, depending on the age of the patient. Because the echo impedances of the coronary artery wall and surrounding adipose tissue are similar, we measured the internal dimensions of the coronary artery. We used a computer assisted video image digitising system (Professional Graphics System, Symtec), which enabled us to measure the distance directly on the video monitor from a magnified image. A part of the echocardiographic image was magnified twice so that one pixel measured 0.1–0.3 mm on the video screen (fig 1). The internal diameter of the aorta was measured on the same view in the axial plane.

A custom made phantom model was created to assess the axial resolution of our equipment (Advanced Technology Laboratories, Ultramark 8) at depths varying from 1 cm to 3 cm with a 7.5 MHz transducer (fig 2). Because the echo impedances of the coronary artery wall and surrounding adipose tissue are similar echoes are reflected effectively only at the interfaces between coronary arterial walls and

the lumen (or blood). The model consisted of a monofilament polypropylene surgical suture (prolene, Ethicon Sutures) placed horizontally in physiological saline. A 7.5 MHz ultrasound transducer (Access C, Advanced Technology Laboratories, 6.4 mm in diameter, 2 cm focus point, 1–4 cm focus zone) was placed 1–3 cm above the suture. The cross sectional image showed the longitudinal axis of the suture. We used minimal gain settings to exclude reverberation echoes. We determined the limits of axial resolution by examining sutures that varied in size from 1 to 4-0 USP (United States Pharmacopeia) (table 3). Two horizontal parallel lines were derived from the upper and lower interfaces of the suture.

We assessed the reliability of the vessel diameter measurement by cross sectional echocardiography in 20 controls. Two observers independently selected frames from recorded videotapes and measured the right coronary artery and aorta twice.

STATISTICAL ANALYSIS

We calculated a regression line and the 95% prediction limits of the right coronary artery and right coronary artery/aorta ratio with the general linear models (GLM) procedure in SAS User's Guide: Statistics (Version 5 Edition, SAS Institute, North Carolina, 1985). Student's *t* tests were performed to assess the differences in the right coronary artery/aorta ratio between groups.

We assessed the repeatability of a measurement from the means and standard deviations calculated for intra-investigator and inter-investigator differences.

Table 3 Diameter of the surgical sutures*

USP size	Metric size (mm)	Limits on average diameter (mm)	
		Minimum	Maximum
1	4	0.40	0.499
0	3.5	0.35	0.399
2-0	3	0.30	0.339
3-0	2	0.20	0.249
4-0	1.5	0.15	0.199

*United States Pharmacopeia XX7, p 1009

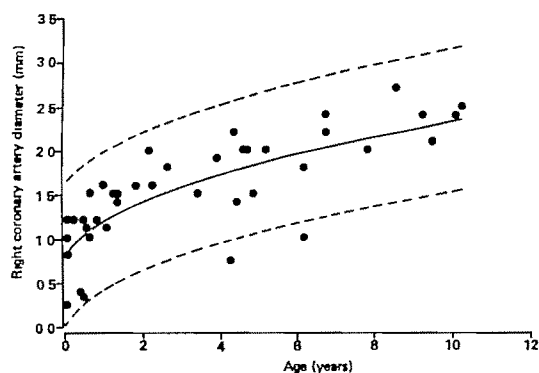


Fig 3 Normal right coronary artery diameters with age by echocardiographic measurement. The regression equation line and 95% prediction limits are given.

Results

RESOLUTION BY PHANTOM MODEL STUDY

When we used the zoom function of the equipment we were able to resolve two parallel lines of a USP size 2-0 suture (0.30–0.339 mm in diameter) with an absolute echo free space between the lines, but we could not resolve two lines for a USP size 0 suture (0.20–0.249 mm in diameter). Therefore the resolution of this system must lie between 0.2 and 0.34 mm. Theoretically, the leading edge method (arrow line A in fig 2) is more accurate for the assessment of vessel diameter; however, in the clinical setting scattered echoes from the surrounding tissue interfere with clear identification of the upper leading edge. For this reason we used the internal dimension of the coronary artery image (arrow line B in fig 2). This method therefore must underestimate the true diameter by 0.2–0.34 mm.

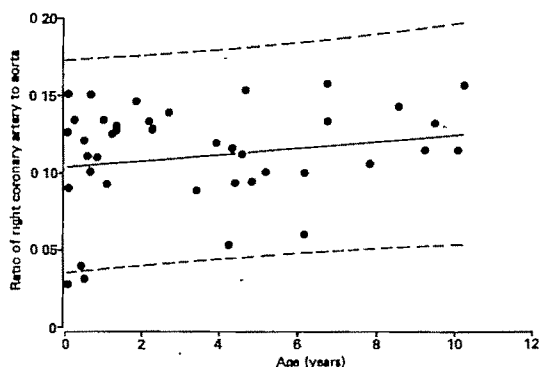


Fig 4 Ratio of right coronary artery to aorta with age by echocardiographic measurement in controls. The mean and 95% prediction limits are given.

Table 4 Normal values of right coronary artery diameter and ratio of right coronary artery to aorta with age

Age	RCA (mm)		RCA/AO	
	Mean	95% upper limit	Mean	95% upper limit
1 mth	0.8	1.6	0.11	0.17
2 mth	0.9	1.7	0.11	0.17
3 mth	1.0	1.8	0.11	0.17
6 mth	1.1	1.9	0.11	0.17
1 yr	1.2	2.0	0.12	0.18
2 yr	1.4	2.2	0.12	0.18
3 yr	1.6	2.4	0.12	0.18
4 yr	1.8	2.6	0.12	0.18
6 yr	1.9	2.7	0.12	0.19
8 yr	2.2	3.0	0.12	0.19
10 yr	2.5	3.2	0.13	0.20

NORMAL RIGHT CORONARY ARTERY DIAMETER

Several linear regression models were fitted for the effect of age and various transformations of age (including log and square root of age) on right coronary artery diameter. The best fit was that between the square root of age and right coronary artery diameter ($p = 0.0001$, $R^2 = 0.62$) (fig 3).

Right coronary artery (mm) = $0.692 + 0.151 \sqrt{\text{age in months}}$, standard error for the estimated slope coefficient = 0.019

Figure 3 gives prediction limits for the normal right coronary arteries. There was no evidence of an age effect on the right coronary artery/aorta ratio ($p = 0.21$, $R^2 = 0.04$) (fig 4): right coronary artery/aorta ratio = $0.104 + 0.00018 (\text{age in months})$, standard error for the estimated slope coefficient = 0.00014. Table 4 lists the calculated means and 95% upper limits of prediction for right coronary artery diameter and right coronary artery/aorta ratio for individual ages.

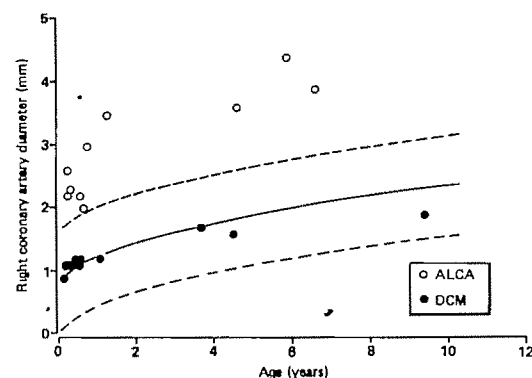


Fig 5 Right coronary artery diameter with age in dilated cardiomyopathy (DCM) and anomalous origin of the left coronary artery from the pulmonary trunk (ALCA) by echocardiographic measurement. The 95% prediction limits of normal are given.

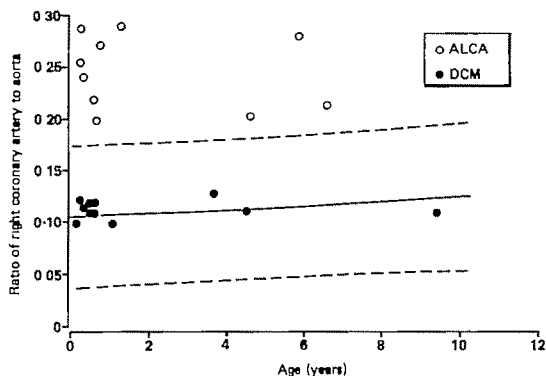


Fig 6 Ratio of right coronary artery to aorta with age in dilated cardiomyopathy (DCM) and anomalous origin of the left coronary artery from the pulmonary trunk (ALCA) by echocardiographic measurement. The mean and 95% prediction limits of normal are given.

DILATED CARDIOMYOPATHY

The right coronary artery and right coronary artery/aorta ratio were all within the normal range in patients with dilated cardiomyopathy (figs 5 and 6). The right coronary artery/aorta ratio ranged from 0.10–0.13 (mean (SD) 0.11 (0.009)).

ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY TRUNK

Direct imaging of the anomalous left coronary artery as it arose from the pulmonary trunk was only possible in five of 10 patients.

The size of the right coronary artery and the right coronary artery/aorta ratio were above the normal range in all patients with anomalous origin of the left coronary artery from the pulmonary trunk (figs 5 and 6). The right coronary artery/aorta ratio ranged from 0.21 to 0.29 with a mean (SD) 0.25 (0.034) that was significantly greater than that in controls and in patients with a dilated cardiomyopathy ($p < 0.001$).

INTRA AND INTER OBSERVER VARIABILITY OF MEASUREMENT

The mean difference between measurements made by the same investigator was 0.0183 (SD = 0.153, range –0.25 to 0.50, SE of a single observation 0.019 mm) for the right coronary artery, and 0.040 (SD 0.295, range –0.60 to –0.70, SE of a single observation 0.040 mm) for the aorta.

The mean difference between measurements by the two investigators was 0.044 (SD 0.148, range –0.18 to 0.40, SE of a single observation 0.024 mm) for the right coronary artery and –0.10 (SD 0.296, range –0.70 to 0.30, SE of a single observation 0.050 mm) for the aorta.

Discussion

DIFFICULTIES IN DISTINGUISHING BETWEEN ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY TRUNK AND OTHER FORMS OF DILATED CARDIOMYOPATHY
Anomalous origin of the left coronary artery from the pulmonary trunk in infants and children is often associated with a dilated cardiomyopathy because the collateral circulation from the right coronary artery is inadequate.^{10,11} Early definitive diagnosis was based exclusively on aortography because clinical findings and ancillary investigations including chest x ray, electrocardiogram,^{8,9} nuclear myocardial scintigraphy,¹² and analyses of left ventricular regional wall motion¹³ did not distinguish this lesion from other forms of infantile dilated cardiomyopathy.

Fisher *et al* reported the first successful direct visualisation of the anomalous origin of the left coronary artery from the pulmonary trunk by cross sectional echocardiography in 1981.⁵ This non-invasive test is much safer than aortography. This is a great advantage because anomalous origin of the left coronary artery from the pulmonary trunk is much rarer than other forms of dilated cardiomyopathy.¹ Although the sensitivity of direct imaging of the anomalous left coronary artery was thought to be adequate, false negative results have subsequently been reported.^{6,7} In particular, it has been difficult to distinguish between the transverse sinus of the pericardium and the proximal portion of the left coronary artery. We believe that echocardiographic visualisation of the origin of the anomalous left coronary artery from the pulmonary trunk is still difficult even when the anomaly is strongly suspected because a child has a dilated poorly contractile left ventricle.

VALUE OF RIGHT CORONARY ARTERY VISUALISATION AND MEASUREMENT IN DIAGNOSING ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY TRUNK

The presence of a tortuous dilated right coronary artery in anomalous origin of the left coronary artery from the pulmonary trunk is well known.^{8,9} It is apparent from this study that either a direct measurement of the right coronary artery or right coronary artery/aorta ratio can be used to distinguish between those patients with anomalous origin of the left coronary artery from the pulmonary trunk and other forms of dilated cardiomyopathy. Patients with anomalous origin of the left coronary artery from the pulmonary trunk always had values greater than the 95% upper limits of prediction. In our series the sensitivity and specificity was 100%.

This approach will miss only those rare cases who have pulmonary hypertension secondary to an associated intracardiac defect. These patients, however, should have normal left ventricular function, because coronary artery flow is preserved.^{14,15} This technique will also identify patients with other diseases associated with a large right coronary artery—such as right coronary arteriovenous fistula, single right coronary artery, Kawasaki disease, or congenital cardiac anomalies with severe right ventricular hypertrophy. We hope that such cardiac causes will be excluded by clinical and echocardiographic examinations.

We are aware of the potential difficulties in obtaining accurate measurements of the right coronary artery diameter through echocardiographic imaging. With experience, however, the method is being successfully applied to normal children and those with Kawasaki disease.¹⁶ At present we believe that all patients with an echocardiographic diagnosis of anomalous origin of the left coronary artery from the pulmonary trunk should have aortography.

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Impaired left ventricular diastolic filling in patients with familial amyloid polyneuropathy: a pulsed Doppler echocardiographic study

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SUMMARY To assess left ventricular diastolic filling in patients with amyloid heart disease 12 patients with familial amyloid polyneuropathy and 15 normal subjects were studied by pulsed Doppler echocardiography. None of the patients had clinical evidence of overt heart disease or restrictive cardiomyopathy and only two of them showed ventricular wall thickening. The peak flow velocity of rapid diastolic filling and the acceleration rate of early diastolic inflow were significantly lower in patients with familial amyloid polyneuropathy than in controls. The pressure half time was significantly longer in patients than in controls. In addition, the peak flow velocity during atrial contraction and the ratio of atrial peak flow velocity to rapid diastolic peak flow velocity were significantly greater in patients than in controls. Although there were no significant correlations between measurements of diastolic filling and clinical findings in patients with familial amyloid polyneuropathy, the ratio of atrial peak flow velocity to rapid diastolic peak flow velocity was significantly related to left ventricular posterior wall thickness.

These findings suggest that in patients with cardiac amyloidosis without restrictive cardiomyopathy, abnormal left ventricular diastolic filling, manifested by a reduction in the rate and volume of rapid diastolic filling with enhanced atrial contraction, can be seen even in the early stage of the disease.

Familial amyloid polyneuropathy causes progressive systemic amyloidosis with polyneuropathy that can affect the heart. Amyloid deposits have been reported in the myocardium when there is no clinically identifiable heart disease or ventricular wall thickening.¹ In earlier serial echocardiographic studies^{1,2} we found that the development of extensive amyloid deposition caused not only progressive increases in ventricular wall thickness but also altered left ventricular systolic and diastolic function. Left ventricular diastolic filling in several cardiac diseases has been non-invasively assessed by pulsed Doppler echocardiography. But so far the profile of left

ventricular diastolic filling in patients with amyloid heart disease has not been precisely established by this technique.³⁻⁵

We have assessed left ventricular diastolic filling in patients with familial amyloid polyneuropathy who had no clinical evidence of overt heart disease.

Patients and methods

PATIENTS

We studied 12 patients with familial amyloid polyneuropathy (seven men and five women, aged 28 to 59 years; mean (SD) 42 (9)) and 15 healthy controls (10 men and five women, aged 27 to 58 years; mean (SD) 40 (10)). All patients were referred to us from several locations in Nagano Prefecture in the central part of Japan⁶ and the diagnosis was based on neurological findings and amyloid deposits in biopsy

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specimens of the stomach, rectum, or sural nerve. None had clinically overt heart disease or restrictive cardiomyopathy or any known concomitant heart disease. The duration of illness ranged from 1.5 to 11 years (mean (SD) 6.2 (3.0)). Biopsy specimens of the right ventricular endomyocardium were taken from eight of the 12 patients and all of them showed histological evidence of amyloid deposition. Each subject gave informed consent at the time of the study.

M MODE AND PULSED DOPPLER ECHOCARDIOGRAPHIC EXAMINATIONS

Cross sectionally guided M mode and pulsed Doppler echocardiograms were obtained with a commercially available cross sectional Doppler echocardiograph (Toshiba, model SSH-40A/SDS-21A), with a 2.4 MHz transducer, at paper speeds of 50 to 100 mm/s. All subjects were examined in the left lateral recumbent position and were in sinus rhythm with heart rate of 62 to 74 beats/min at the time of the study.

In the M mode echocardiographic examination, the following variables were measured according to the criteria recommended by the American Society of Echocardiography⁷: (a) left ventricular end diastolic and end systolic dimension and (b) left ventricular

posterior wall thickness at end diastole. All measurements were made in at least three cardiac cycles and averaged with the aid of a computer interfaced graphic analyser (Kontron, model Cardio-200). Then fractional shortening was calculated.

Doppler recordings of transmitral flow velocity were taken through an apical four chamber view with the Doppler cursor oriented parallel to the long axis plane of the left ventricle and the sample volume carefully placed at the level of the mitral annulus (fig 1). The following measurements were obtained (fig 2): (a) peak flow velocity of left ventricular rapid diastolic filling (peak E), (b) peak flow velocity during atrial contraction (peak A), (c) the ratio of peak A to peak E, (d) acceleration rate of left ventricular early diastolic flow, (e) acceleration time of early diastolic flow, and (f) pressure half time, which is defined as the time from peak E to peak E/ $\sqrt{2}$.⁸

STATISTICAL ANALYSIS

Data are expressed as mean (SD) and were analysed by an unpaired *t* test. Correlations between measurements derived from Doppler echocardiography and clinical and M mode echocardiographic findings were assessed by linear regression analysis. Statistical significance was assumed when the *p* value was < 0.05.

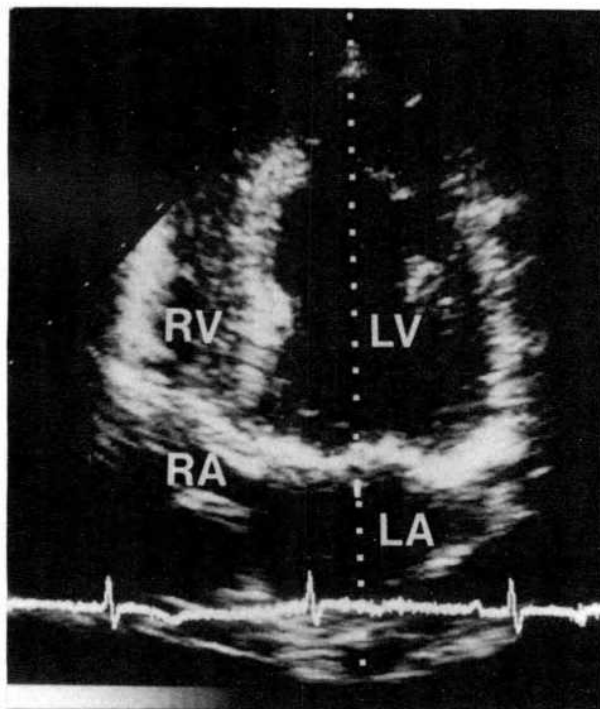


Fig 1 Stop frame cross sectional echocardiogram in the apical four chamber view showing the typical position of the pulsed Doppler sample volume used to obtain left ventricular diastolic flow-velocity waveforms. The sample volume is positioned just below the mitral valve annulus. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

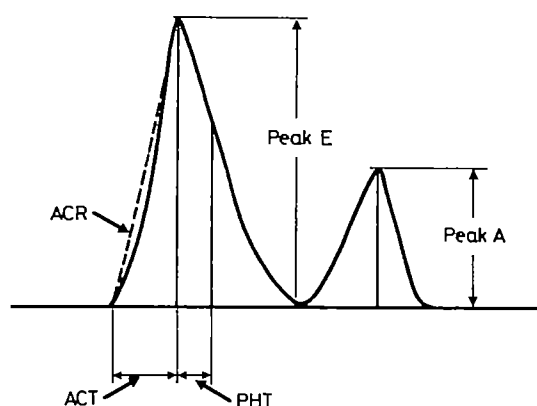


Fig 2 Measurement of the left ventricular inflow pattern. ACR, acceleration rate of left ventricular early diastolic flow; ACT, acceleration time of left ventricular early diastolic flow; PHT, pressure half time; peak A, peak flow velocity during atrial contraction; peak E, peak flow velocity of left ventricular rapid diastolic filling.

Results

M MODE ECHOCARDIOGRAPHIC FINDINGS

Table 1 shows that the age and sex distribution, heart rate, left ventricular cavity size, and fractional shortening were similar in patients with familial amyloid polyneuropathy and in controls. Although 10 (83%) of the 12 patients had normal left ventricular posterior wall thickness, this was slightly but significantly greater in patients than in controls.

PULSED DOPPLER ECHOCARDIOGRAPHIC FINDINGS

The peak E during rapid diastolic filling and the acceleration rate of early diastolic flow in patients with familial amyloid polyneuropathy were 39 (9) cm/s and 352 (73) cm/s², compared with 51 (11) cm/s ($p < 0.01$) and 514 (130) cm/s² ($p < 0.001$) in controls, respectively. The pressure half time was

Table 1 Clinical characteristics of patients with familial amyloid polyneuropathy (FAP)

	FAP	Controls	p value
Number	12	15	
Age (mean (SD))	42 (9)	40 (10)	NS
Male/female	7/5	10/5	
Duration of illness (yr)	6.2 (3.0)		
HR (beats/min)	64 (4)	66 (4)	NS
EDD (mm)	46 (4)	48 (4)	NS
ESD (mm)	31 (6)	32 (4)	NS
PWT (mm)	9.6 (2.9)	8.3 (0.6)	< 0.05
%FS (%)	36 (5)	38 (4)	NS

EDD, end diastolic diameter; ESD, end systolic diameter; %FS, percentage fractional shortening; HR, heart rate; PWT, left ventricular posterior wall thickness.

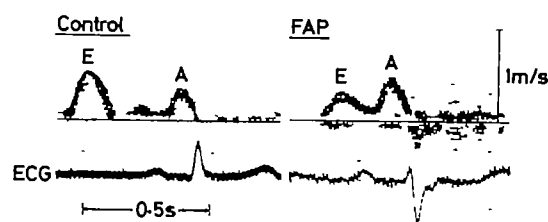


Fig 3 Pulsed Doppler waveform of left ventricular diastolic flow velocity. Left panel, from a 41 year old control with peak flow velocity of left ventricular rapid diastolic filling (E) higher than peak flow velocity during atrial contraction (A). Right panel, from a 38 year old patient with familial amyloid polyneuropathy (FAP) with A higher than E. ECG, electrocardiogram.

significantly longer in patients than in controls (70 (8) v 52 (10) ms, $p < 0.001$). The peak A during atrial contraction and the ratio of peak A to peak E were significantly greater in patients than in controls (42 (6) v 30 (7) cm/s, $p < 0.001$ and 1.14 (0.28) v 0.62 (0.19), $p < 0.001$, respectively) (fig 3 and table 2). Of the 10 patients without ventricular wall thickening, nine showed abnormal left ventricular diastolic filling. These included reduced peak E in seven patients, decrease in the acceleration rate of early diastolic flow in five, prolonged pressure half time in nine, enhanced peak A in seven, and increased ratio of peak A to peak E in eight.

Although there were no significant correlations between measurements of left ventricular diastolic filling and heart rate, left ventricular cavity size, or fractional shortening, the ratio of peak A to peak E was significantly related to left ventricular posterior wall thickness ($r = -0.66$, $p < 0.05$). In addition, no measurement correlated significantly with age and duration of illness, though the frequency and magnitude of abnormalities in peak E, peak A, and the ratio of peak A to peak E tended to increase with age and duration of illness (figs 4 and 5).

Discussion

Our results show that in patients with familial amyloid polyneuropathy an abnormal pattern of left ventricular diastolic filling is detected by transmitral

Table 2 Mean (SD) Doppler flow measurements

Measurement	FAP	Controls	p value
Peak E (cm/s)	39 (9)	51 (11)	< 0.01
Peak A (cm/s)	42 (6)	30 (7)	< 0.001
Peak A/Peak E	1.14 (0.28)	0.62 (0.19)	< 0.001
ACR (cm/s ²)	352 (73)	514 (130)	< 0.001
ACT (ms)	108 (19)	104 (25)	NS
PHT (ms)	70 (8)	52 (10)	< 0.001

See fig 2 for abbreviations

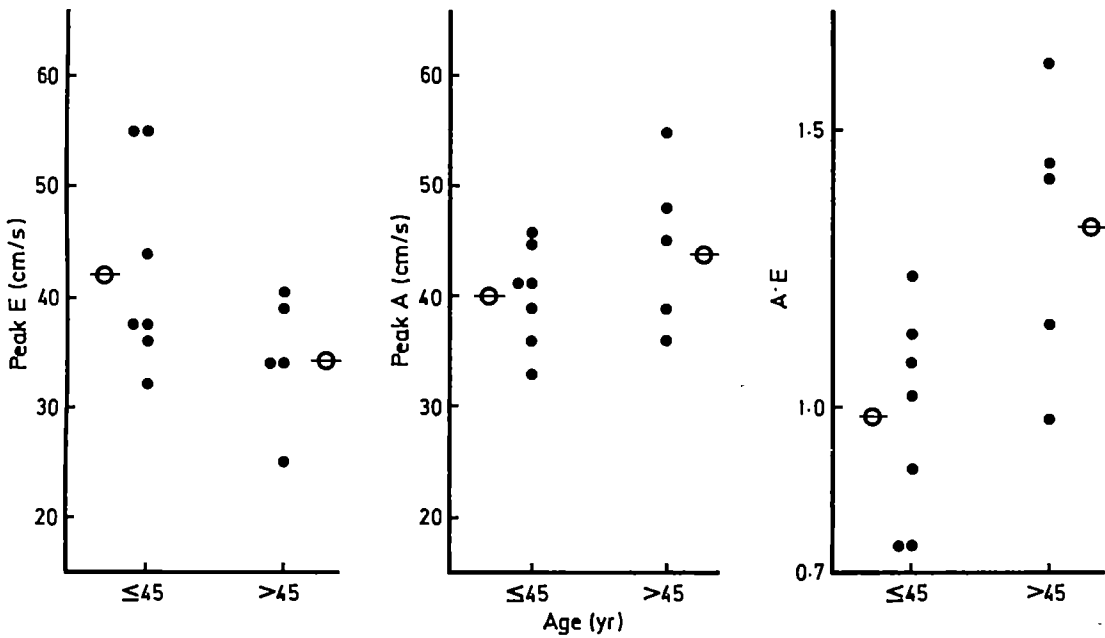


Fig 4 Comparison of measurements of left ventricular filling between patients with familial amyloid polyneuropathy aged ≤ 45 and > 45 (peak flow velocity of left ventricular rapid diastolic filling (peak E), peak flow velocity during atrial contraction (peak A), and the ratio of peak A to peak E (A:E)). Mean values are also given.

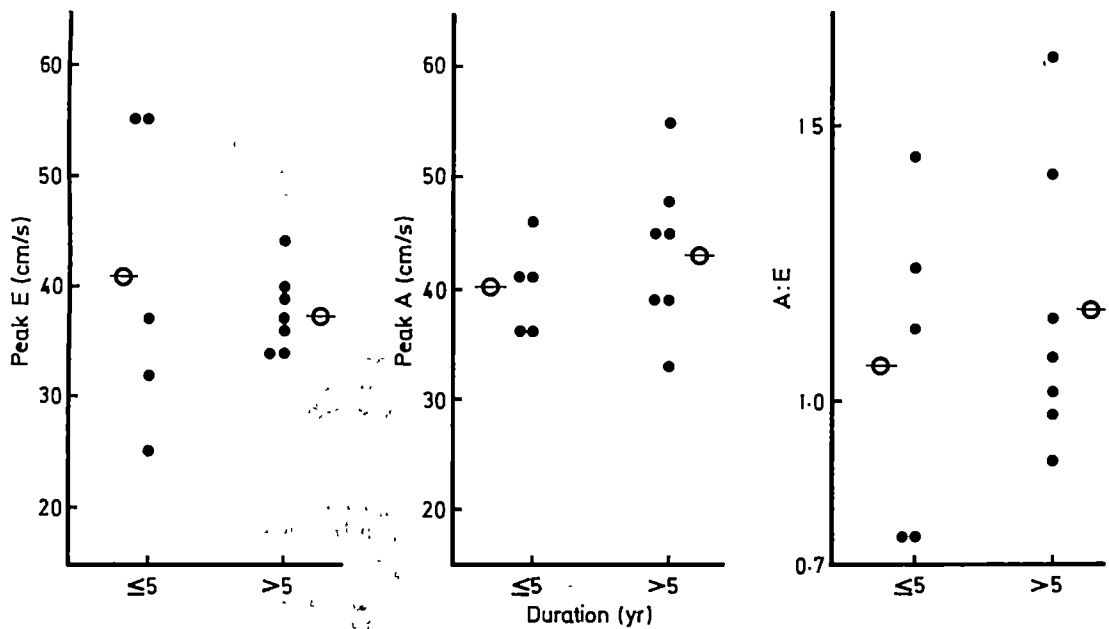


Fig 5 Comparison of measurements of left ventricular filling between patients with familial amyloid polyneuropathy who had been ill for less than five years and those ill for more than five years (peak E measurements, peak A measurements, and ratio of peak A to peak E (A:E) measurements). Mean values are also given.

flow velocity and that this can be identified even in the absence of clinically overt heart disease, ventricular wall thickening, and abnormal systolic function. Our results also show that abnormalities in diastolic filling increase with age and the duration of illness in patients with familial amyloid polyneuropathy.

LEFT VENTRICULAR DIASTOLIC FILLING IN PATIENTS WITH AMYLOID HEART DISEASE

Numerous invasive and non-invasive studies have shown that left ventricular diastolic filling is invariably impaired in patients with amyloid heart disease. Catheter studies showed an accelerated rapid diastolic filling followed by a cessation of filling in mid to late diastole in patients with amyloid restrictive cardiomyopathy.^{9,10} But uniformly depressed filling was reported in some patients in the absence of a dip and plateau pattern in left ventricular pressure recordings.^{10,11} Recently St John Sutton *et al* used digitised M mode echocardiography to show a prolonged isovolumic relaxation time and reduced peak filling rate of rapid diastolic filling in patients with primary and myeloma associated amyloidosis.¹² More recently, a range of abnormalities in left ventricular diastolic filling has been reported in patients with amyloid heart disease studied by pulsed Doppler echocardiography. In patients without obvious echocardiographic evidence of myocardial involvement, impaired relaxation of the left ventricle was manifested by a decrease in the rate and volume, as well as a prolongation of rapid filling and enhanced atrial systolic filling.^{4,5} On the other hand, in patients with increased chamber stiffness with resultant restriction of diastolic filling, rapid filling rate was increased and was accompanied by normal or reduced atrial systolic filling of the left ventricle.^{3,5} Thus both types of abnormal diastolic filling seem to be present to variable degrees in patients with amyloid heart disease.

In our study an abnormal pattern of left ventricular diastolic filling was detected in many patients with familial amyloid polyneuropathy and was characterised by a reduction in the rate and volume as well as a prolongation of rapid diastolic filling with exaggerated atrial systolic filling. In most of our patients amyloid heart disease was in the early stages¹²; none of them showed clinically overt heart disease, restrictive cardiomyopathy, or abnormal fractional shortening and most had normal ventricular wall thickness. Our Doppler findings were consistent with those of Plehn *et al*⁴ and Klein *et al*,⁵ in which patients had no evidence or slight echocardiographic evidence of myocardial involvement. Our results also confirmed that abnormal left ventricular diastolic filling can be seen before the

development of clinically overt heart disease, left ventricular wall hypertrophy, or abnormal systolic function.^{1,13}

In our study only the ratio of peak A to peak E correlated significantly with the thickness of the left ventricular posterior wall, while individual peak velocities or other clinical findings did not. Although the flow direction at the centre of the mitral orifice might be assumed to be perpendicular to the mitral annulus, it was difficult to be certain that the apical view showed the true alignment of the mitral annulus. This might explain why only the ratio of peak A to peak E, which eliminated this factor, correlated with the wall thickness. In patients with amyloid heart disease, ventricular wall hypertrophy has generally been reported to be caused by amyloid infiltration into the myocardium as well as resultant fibrosis.^{14,15} We did not measure the extent of amyloid infiltration or fibrosis in any of our patients.

We believe that the mechanism for abnormal diastolic filling in this disorder is likely to be abnormal left ventricular distensibility related to interstitial accumulation of amyloid and collagen. Furthermore, myocardial ischaemia may also lead to abnormalities in diastolic filling; several necropsy studies showed amyloid deposits in the intramural coronary arteries in patients with cardiac amyloidosis.^{14,16-18}

CLINICAL IMPLICATIONS

We found age related changes in peak E, peak A, and the ratio of peak A to peak E in patients with familial amyloid polyneuropathy. Moreover, abnormalities in these measurements increased with the duration of illness. So these factors must be considered when assessing diastolic events in patients with familial amyloid polyneuropathy.

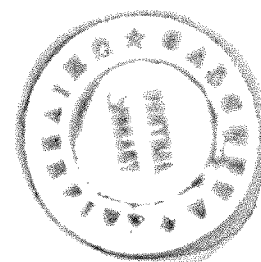
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Familial aortic dissection: a report of rare family cluster

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SUMMARY Acute aortic dissection occurred in three of four siblings without Marfan syndrome. All of them were successfully treated by operation and remain well 6-42 months after operation. Their mother died suddenly in another hospital of acute aortic dissection. All her siblings were dead and cardiovascular disease was suspected in all of them.

Aortic dissection is a relatively common catastrophic disease, but it is unusual to find the disease in four close relatives—three siblings and their mother.

Patients and methods

CASE 1

This 31 year old Japanese man (the second son) who was 170 cm tall and weighed 66 kg was brought into the emergency room with severe pain in the back and right leg on 8 January 1984. He had no previous history of these symptoms. Cyanosis was evident and there was no right radial pulse. Arterial pressure (146/72 mm Hg on arrival) quickly fell to 60/30 mm Hg. There was an audible regurgitant murmur (3/6) of the aortic valve. Cross sectional echocardiography showed a flapping movement in the ascending aorta. The aortic annulus was 3.0 cm in diameter. There was no evidence of mitral valve abnormality. An emergency operation was performed. An intimal tear was identified at 3 cm above the sinotubular junction and three quarters of the aortic circumference was dissected. The aortic valve commissures were suspended with pledgetted sutures and the transected aorta was reinforced with Teflon felt and anastomosed together. Several hours after the patient was transferred to the intensive care unit urine flow ceased and serum potassium began to rise. Emergency haemodialysis was started and was maintained every other day for three weeks until renal function returned to normal. After postoperative rehabilitation the patient was discharged four months after operation. In the outpatient clinic after discharge a physical examination was performed to

rule out Marfan syndrome. The ratio of the upper segment to the lower segment was 1.3, the arm span was 162 cm, and the metacarpal index was 7. Thumb sign and wrist sign were negative and the lens were normal. The greatest anterior-posterior measurement of the thorax was 23 cm and of normal shape.

CASE 2

The elder brother of case 1, who was 34 years old, 167 cm tall and weighed 67 kg, walked into the emergency room on 18 May 1984 with mild chest

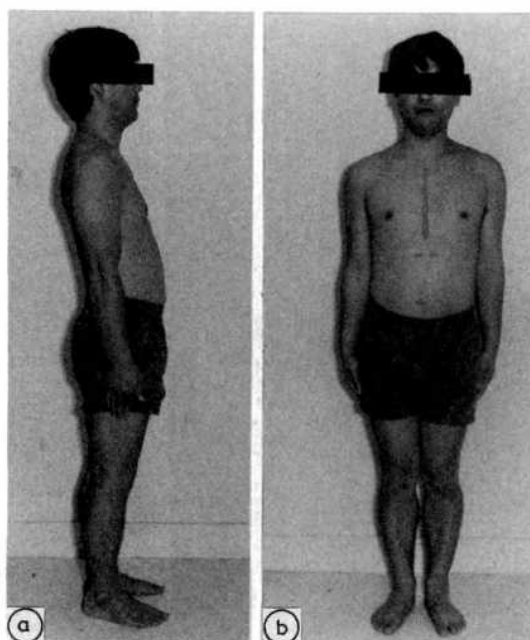


Fig 1 Photograph of case 2.

Requests for reprints to Dr Masaaki Toyama, Department of Cardiovascular Surgery, Kameda General Hospital, 929 Higashi-cho Kamogawa City, Chiba, 296 Japan.

Accepted for publication 22 September 1988



Fig 2 Aortogram of aortic root in case 3 showing the typical shape of annuloaortic ectasia.



Fig 3 Aortogram of aortic root of case 4 also showing the typical shape of annuloaortic ectasia with appreciable aortic regurgitation.

pain and headache that had developed that morning. An aortic regurgitant murmur was audible. Echocardiography and computed tomography showed a DeBakey type I dissection. The aortic annulus was 3.2 cm in diameter and mitral valve prolapse was not evident. Examination of the eyes showed no evidence of abnormality except for moderate myopia. The skeletal system was apparently normal. The arm span was 156 cm, the upper segment to lower segment ratio was 1.33, the metacarpal index was 6.6, and the thumb sign and wrist sign were negative. Chest x rays and studies of pulmonary function were normal. Because haemodynamic function remained stable and chest pain was controlled with medication, operation was performed three weeks later on a semielective basis. The ascending aorta was dilated to an aneurysmal degree and there was an intimal tear 2 cm distal to the sinotubular junction. The aortic valve commissures were resuspended and a huge aneurysm was replaced with woven graft. Apart from the development of postoperative psychosis the postoperative course was uneventful. He was discharged 50 days after operation. Figure 1 shows a photograph of this patient.

CASE 3

The 39 year old sister of cases 1 and 2 was brought to the emergency room by ambulance on 14 January 1987 with a one day history of lumbago and epigastric



Fig 4 Abdominal aortography in case 4 showing a dissected intimal flap.

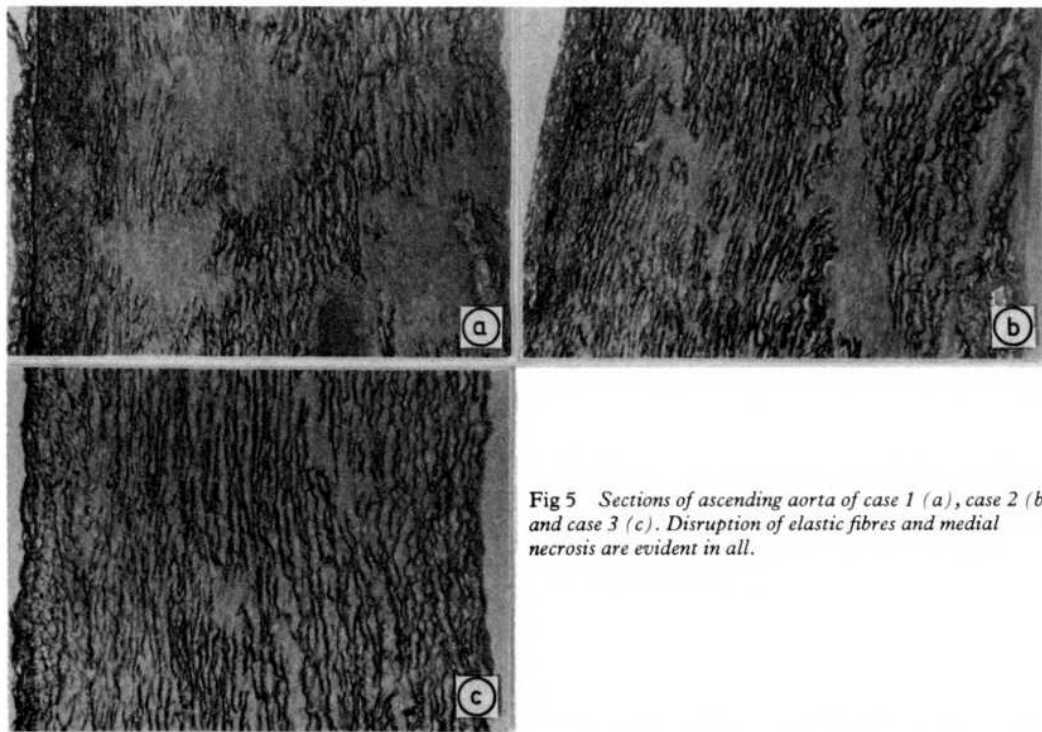


Fig 5 Sections of ascending aorta of case 1 (a), case 2 (b), and case 3 (c). Disruption of elastic fibres and medial necrosis are evident in all.

pain. Because of her family history, aortic dissection was suspected. Echocardiography and aortography confirmed a DeBakey type I dissection. The aortography also showed typical evidence of annulo-aortic ectasia (fig 2) (diameter 3.6 cm). The mitral valve did not show any evidence of abnormality. Emergency surgery was performed. The gross anatomy of dissected aorta was almost identical with those of her brothers. She did well after operation and was discharged on the 23rd postoperative day.

She was examined as an outpatient. The ratio of the upper segment to the lower segment was 1.31, her arm span was 130 cm, and she was 142 cm tall. The metacarpal index was 6.8 and the thumb and wrist signs were negative. Her lenses, fundi, and visual acuity were normal.

CASE 4

The mother of our patients died aged 55 in another hospital in 1978. According to the information we obtained, she was admitted complaining of shortness of breath on exertion and with anorexia. On admission, she was 153.4 cm tall and weighed 42.2 kg; she did not have a history of hypertension. She was known to have normal vision but there was no further information on her eyes. Cardiac catheterisation showed annuloaortic ectasia with grade 2 aortic

regurgitation (fig 3) and type III aortic dissection (fig 4). The diameter of the ascending aorta was 5.6 cm and that of the aortic annulus was 3.9 cm. Gastrointestinal investigation disclosed advanced stomach cancer. She died suddenly soon afterwards. The family refused permission for a necropsy.

Discussion

There are eleven previous reports of familial aortic dissection.¹⁻¹¹ Nine of the 23 family members had features suggestive of Marfan syndrome but in 14 patients it was not clear if they had Marfan syndrome. Half of these cases were reported before medical and surgical treatment for acute aortic dissection was available and 21 of the 23 patients died. Necropsy was performed in most patients and showed a tear in the ascending aorta in 15 patients and in the descending aorta in six.³⁻¹⁰ Histological examination was carried out in 17 patients and there was medial necrosis in 16. Only one had a normal histology of aorta.¹¹

Our three patients are most unusual because none of the family had features of the Marfan syndrome or a history of hypertension and all three survived and were rehabilitated after emergency operation. Histological examination of the aorta showed disruption of elastic fibres and medial necrosis in all three

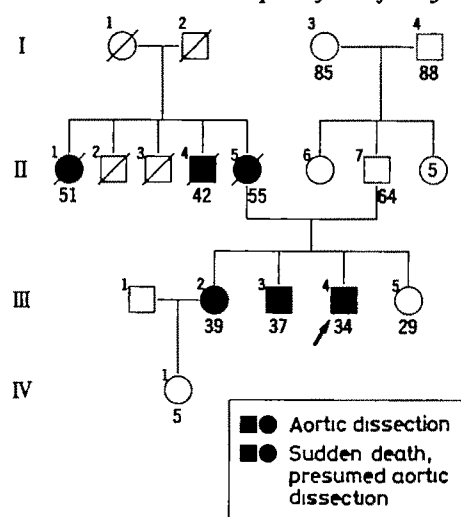


Fig 6 Family pedigree. Squares and circles are males and females respectively.

patients (fig 5). Nobody from the mother's family is alive and a cardiovascular cause of death was suspected in almost all of them. All members of the father's family are alive and well (fig 6). There was no intermarriage. The youngest sister is 29 and at present does not show any signs of aortic dissection. She will be examined by echocardiography every year to detect enlargement of the aortic annulus and aorta. If an aortic aneurysm is found it can be operated on to prevent dissection. There is a 50:50 risk of her being affected.

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Case report

Coronary ostial stenosis after radiotherapy: angioplasty or coronary artery surgery?

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From the Departments of *Cardiology, †Cardiac Surgery, and ‡Radiotherapy, Middlesex Hospital, London

SUMMARY A thirty year old man underwent coronary angioplasty for an isolated ostial stenosis of the ostium of the right coronary artery after mediastinal radiotherapy given ten years previously. Despite an angiographically acceptable angioplasty result, he had a myocardial infarction two months later and coronary artery surgery was performed.

The most effective form of myocardial revascularisation for radiotherapy related coronary artery lesions remains to be established.

Pericardial disease is the most frequent cardiac complication of radiotherapy, but coronary artery lesions, myocardial fibrosis, and conduction disorders are also recognised.^{1,2} We report a rare coronary lesion—an isolated stenosis of the ostium of the right coronary artery—in a young man who had been treated with radiotherapy 10 years before. The patient underwent angioplasty but later sustained a myocardial infarction and coronary artery surgery was performed.

Case report

In 1976 when he was 20, a white man presented with left supraclavicular and right axillary lymphadenopathy. After a staging laparotomy and lymph node biopsy, stage IIA mixed cellularity Hodgkin's disease was diagnosed. He was treated with radiotherapy to a mantle field and initially had 6 Gy (600 rad) in two fractions to the mid-mediastinum and six weeks later received 40 Gy (4000 rad) given in 20 fractions over 28 days to the mid-mediastinum. The radiotherapy was administered as a single anterior radiation field by a telecobalt machine. Since then, he has remained in complete remission and has never been treated with cytotoxic drugs.

In 1978 he developed bilateral pleural effusions

and a pericardial effusion with cardiac tamponade. Bloodstained pericardial fluid (760 ml) was aspirated but investigations showed no evidence of pericardial infection or malignancy. In May 1979 he presented with pleurisy, and cytological examination of the pleural fluid showed pleomorphic cellular deposits with atypical lymphoid cells, plasma cells, and eosinophils but no Reed-Sternberg cells. After aspiration of the effusion, the chest x ray showed bilateral upper zone fibrosis and elevation of both hila.

In November 1979 he developed pericardial pain associated with another small pericardial effusion which resolved spontaneously. Recurrent small pleural and pericardial effusions were diagnosed in March 1980 and computerised tomography of the chest showed paramediastinal fibrosis but no lymphadenopathy. The pericardial fluid was straw coloured and yielded no malignant cells.

In July 1980 he presented with shock due to cardiac tamponade and underwent emergency pericardiotomy and a pericardial window was made. One litre of pericardial fluid was withdrawn. Pericardial biopsy showed fibrous tissue, reactive mesothelium, and focal aggregates of lymphoid and plasma cells with the occasional neutrophil cells but no malignant cells.

During the next six years the patient was well enough to play tennis and lead an active life. In November 1986 while walking to work he developed severe bilateral arm and interscapular pain, vomited,

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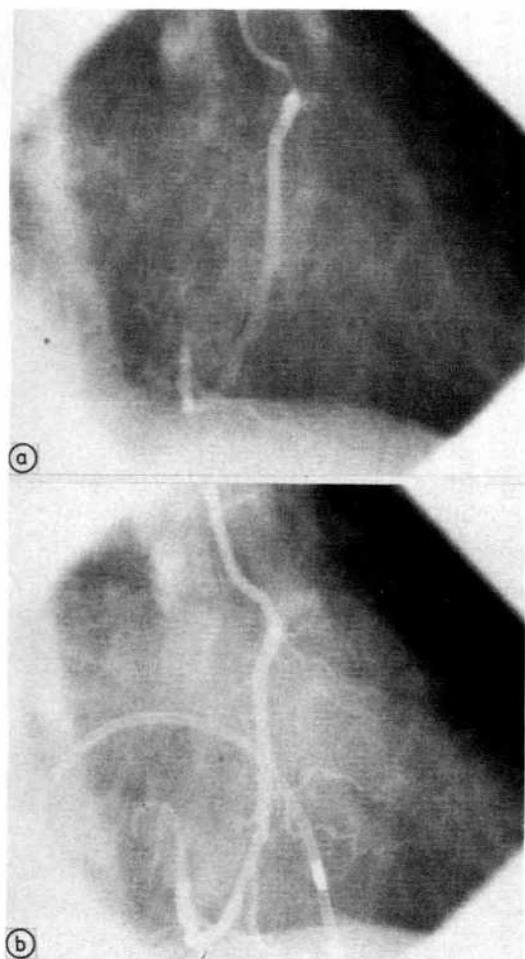


Fig 1 (a) Right coronary artery ostial stenosis before angioplasty. (b) Right coronary artery ostial stenosis after angioplasty.

and collapsed unconscious. The electrocardiogram showed widespread ST and T wave inversion. Serial measurements of cardiac enzymes were normal. He had no risk factors for coronary artery disease. Computed tomography of his chest showed no aortic dissection or relapse of his Hodgkin's disease. Coronary angiography and left ventriculography showed only an isolated stenosis of the right coronary ostium (fig 1a), which was not reversed by intracoronary nitrates or oral nifedipine. He was limited by fatigue and angina after nine minutes on the Bruce treadmill protocol and developed 4 mm of ST depression with a fall in systolic blood pressure at peak exercise.

Exercise thallium-201 myocardial scintigraphy showed a reversible perfusion defect in the inferior

wall of the left ventricle. Coronary angioplasty of the right coronary ostial stenosis was performed with a 3.5 mm balloon. It produced a fall in the transtenotic gradient from 45 to 15 mm Hg and a satisfactory angiographic result (fig 1b). Two days later he completed 11 minutes on the Bruce treadmill exercise protocol, was limited by fatigue, and developed 3 mm of ST depression in leads V1-V3 (fig 2a and b) without angina. Repeat exercise thallium-201 myocardial scintigraphy again showed a reversible perfusion defect in the inferior left ventricular wall. Nifedipine was prescribed and he was discharged from hospital. Two months after angioplasty, in January 1987, he presented with an inferior Q wave myocardial infarct. Coronary angiography showed near total occlusion of the right coronary artery and inferior left ventricular hypokinesia. Because of continuing post-infarction angina and exercise induced reversible myocardial ischaemia, saphenous vein coronary artery bypass grafting to the right coronary artery was performed in April 1987. At operation, dense adhesions were found all around the heart and the pericardium was grossly thickened. The patient made an uneventful recovery and remains symptom free.

Discussion

Cardiac complications of radiotherapy are dose related and may not become apparent for several years. Because patients with serious neoplasms may die before cardiac complications are manifest, the true incidence of radiotherapy related coronary artery disease is difficult to determine but has been estimated as about 6%.³

Except in young patients without recognisable risk factors for coronary artery disease, it may be difficult to incriminate radiotherapy as the sole cause of coronary artery lesions. We believe that radiotherapy was the most likely cause of our patient's coronary artery lesion for several reasons: he was young and had no risk factors for atheromatous coronary artery disease, the appearance of the pericardium at operation, the large total dose of radiation administered (the dose to the right coronary artery was estimated to be 55 Gy owing to the use of a single anterior field), and the proximal site of the lesion.² In addition, an isolated coronary ostial lesion is a rare lesion in atheromatous coronary artery disease and it occurs predominantly in young and middle aged women.

We are aware of 39 reported cases of coronary ostial stenoses.^{4,5} These were associated with radiation, syphilis, Takayasu's aortitis, congenital anomalies of the coronary arteries, hypercholesterolaemia, and as a complication of coronary angiography.

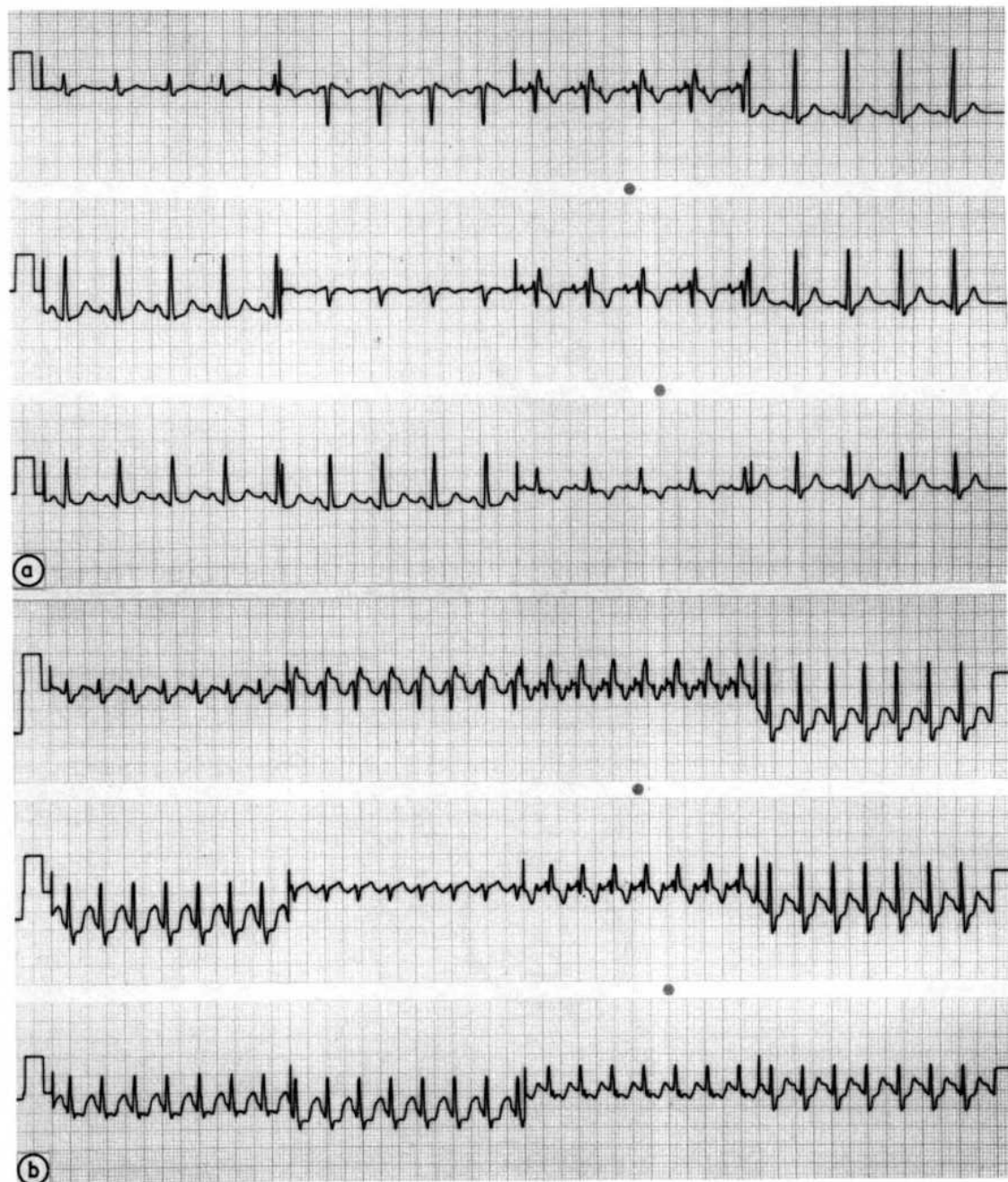


Fig 2 12 lead electrocardiogram recorded at rest after angioplasty. (b) 12 lead electrocardiogram recorded at peak exercise after angioplasty showed 2 mm of ST segment depression in leads II, III, aVF, and V3-V6.

The mechanism of radiation induced coronary artery disease is unclear. Animal studies with electron microscopy have shown damage to the cytoplasm of the capillary endothelial wall.⁶ This may

lead to degeneration of the cell with thrombosis or capillary rupture (or both) and possibly with endothelial proliferation and a tendency for thrombosis. The characteristic histological appearance is that of

pure intimal fibrosis (although there may be adventitial fibrosis), most often without foam cells, cholesterol clefts, or extracellular lipid deposits.²

We are aware of two other reports of the use of angioplasty in coronary artery lesions presumably related to radiotherapy, but neither report provides follow up details. Nakhjavan *et al* performed angioplasty for an ostial stenosis of the right coronary artery in a 54 year old man⁷ and Sande and colleagues reported the use of angioplasty to a lesion of the mid-portion of the left anterior descending coronary artery in a 50 year old woman with hypercholesterolaemia.⁸

Saphenous vein coronary artery bypass grafting has been performed for radiotherapy related stenosis of the coronary artery ostium.⁹ It is possible that radiation damage to the internal mammary arteries may make this form of myocardial revascularisation technically difficult, but we are unaware of information on this surgical approach in this condition. Our patient sustained a myocardial infarction associated with a slight residual stenosis of the ostium of the right coronary artery. Because of technical problems associated with angioplasty for ostial stenoses and the nature of radiotherapy related lesions, coronary artery surgery may be a more effective form of revascularisation for these lesions.

With the improving survival of patients with mediastinal tumours relating from radiotherapy, recognition and appropriate management of potential cardiac complications are important; however, the optimal management of radiotherapy related coronary artery lesions remains to be established.

We are grateful to Dr Howard Swanton, Mr M F Sturridge, and Dr A Jelliffe for help in preparing this report.

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Correspondence

Correcting a block?: successful experience of a small British pacing centre

Sir,

I am concerned that the report by Dr Godden and his colleagues of a small British pacing centre (1987;58:495-8) which describes the exclusive use of single chamber demand (VVI) pacing does not justify its conclusion that the mode "is the system of choice for most elderly sedentary patients", especially as a considerable proportion of patients were suffering from breathlessness and tiredness, for which physiological pacing modes have been shown to be superior.^{1,2} Their patients' average age was 74—little older than those in other published series.

Age is no bar to the optimum treatment of tiredness and breathlessness. We are given no information about the distribution of tiredness and none on the frequency of breathlessness, except when it is the major symptom. Even more unsatisfactory in their report is the syphoning off of patients to other centres if a "more complex system was required"; there is no indication of numbers, reasons, or ages and this feature must negate their conclusion about the use of VVI pacing. Also of concern is their decision to use VVI pacing in sinus node disease (no information on how many patients) despite its well documented inferiority and association with several complications.^{3,4}

Finally, we are given extremely limited information about the investigation undertaken to arrive at the choice of pacing mode. We are told (in the discussion and not in the methods or results) that 24 hour ambulatory monitoring was undertaken in 37 out of 100 and that it influenced the decision. We do not know what it showed, how it influenced the decision, or whether it influenced decisions on how to pace. What about the use of simple electrophysiology, trial of pacing, exercise testing, etc? If one is seeking to improve symptoms other than syncope or presyncope some or all of these investigations are often required if patients are to get the best treatment. There might even be a cost advantage in the long run in using a more expensive pacemaker with less medication.

Simon Joseph,
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This letter was shown to one of the authors, who replies as follows:

Sir,

I thank Dr Joseph for his comments. Regrettably he misquotes our paper. The statement "VVI pacing probably remains the system of choice for most elderly patients" was not the conclusion of our paper. We attempted to show that a pacing centre in a district general hospital increases the implant rate in the area served by the hospital. The comment on suitability of VVI pacing for the sedentary elderly was clearly attributed to another author.¹ Our study was not designed to assess the efficacy of different pacing modes.

I can reassure Dr Joseph that "syphoning off" of patients to specialist centres for more complex pacing systems was rare. During the study period one 40 year old man was referred to be considered for dual chamber pacing and received a single electrode rate responsive system. A 70 year old woman required a

VVI system (not implanted at our centre) to be changed to a dual chamber system as a result of pacemaker syndrome. A 52 year old woman required insertion of an anti-tachycardia pacemaker for treatment of Wolff-Parkinson-White syndrome with reciprocating tachycardia.

Fifteen patients with sick sinus syndrome were paced. They had a mean age similar to the study group (72 years) and there was only one death during the follow up period.

Ambulatory monitoring was used to establish a relation between electrocardiographic findings and symptoms, particularly in patients with the sick sinus syndrome and those with atrial fibrillation. Electrophysiological studies and stress testing were not performed.

I am aware of the scientific work showing the advantage of dual chamber over VVI pacing for exercise tolerance. It remains to be seen whether dual

chamber pacing will be widely adopted to pace the sedentary elderly in the United Kingdom. A cautious acceptance is likely until community, as well as laboratory studies, establish the ability of dual chamber pacemakers to improve not only survival, but also the quality of life.

Dr Joseph's point about the cost advantage of more expensive pacing systems, must for the present, remain speculative.

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Raigmore Hospital,
Inverness IV2 3UJ.

Reference

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Notices

British Cardiac Society

The Annual General Meeting for 1989 will take place in Oxford on 6 and 7 April 1989, and the closing date for receipt of abstracts was 6 January 1989.

Diagnostic and therapeutic cardiac catheterisation

A medical education programme of the American College of Cardiology on Advances in Diagnostic and Therapeutic Cardiac Catheterization will take place in Fort Lauderdale, Florida, on 3 to 5 March 1989. For further information write to Margaret Sgro, Extramural Programs Department, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, Maryland 20814, USA.

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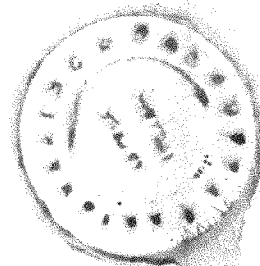
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Cardiopulmonary response to dynamic exercise after heart and combined heart-lung transplantation

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SUMMARY The exercise capacity and cardiopulmonary response to progressive dynamic exercise of eight healthy recipients of heart-lung transplants were compared with those of matched recipients of orthotopic cardiac transplants and normal controls. In both transplant groups the maximum workloads were lower than that in the normal group. The transplant recipients had higher pre-exercise heart rates and lower maximum heart rates than the normal controls. Ventilation during submaximal exercise was similar in the heart transplant group and the controls. The heart-lung group had an increased ventilatory response associated with lower end tidal carbon dioxide concentrations.

Exercise capacity after combined heart-lung transplantation is similar to that after cardiac transplantation. Transplant recipients have an abnormal heart rate response during exercise related to cardiac denervation. The altered ventilatory response in heart-lung recipients may be the result of pulmonary denervation.

Combined heart-lung transplantation is a therapeutic option for patients with end stage pulmonary vascular disease¹ and parenchymal lung disease.² Successful transplantation can relieve symptoms and improve the patient's quality of life.³ However, exercise capacity after transplantation is below predicted values⁴ and the physiological consequences of this extensive operation have not been fully evaluated.

We compared the exercise capacity and cardiopulmonary response to exercise of a group of healthy recipients of heart-lung transplants with that of cardiac transplant recipients and normal controls.

Patients and methods

We studied eight recipients of heart-lung transplants who were free of cardiopulmonary complications (with the exception of treated hypertension). They were compared with eight normal individuals and eight recipients of cardiac transplants who were matched as closely as possible for age and sex. The transplant recipients were also matched for time after

operation. Table 1 shows the characteristics of the three groups; predicted values for lung function tests, calculated for the anthropometric characteristics of the subjects, were obtained from Quanjer.⁵ All the transplant recipients were well at the time of the study with no clinical evidence of rejection of the heart or lungs. All had clear chest radiographs and stable lung function tests. None had evidence of cardiac rejection on the most recent endomyocardial biopsy specimen. Table 1 shows the drug treatment in the transplant recipients.

The normal controls were well, had no symptoms or previous history of cardiopulmonary disease, and were not receiving any drug treatment. People who undertook regular exercise training were excluded. The study protocol was approved by the District ethics committee and informed consent was obtained from all subjects.

METHODS

Exercise tests were performed on an electronically braked cycle ergometer (Lode, Groningen, the Netherlands). The subjects were kept at rest, seated on the exercise bike, for five minutes before data collection started. The study consisted of two minutes' data collection at rest followed by a period of exercise in which the workload was increased by 10 W every

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Table 1 Characteristics of study groups

	Age (yr)	Sex	Height (m)	Weight (kg)	Pretransplant diagnosis	Donor age (yr)	Donor sex
<i>Heart-lung transplant</i>							
1	44	F	1.63	67	Eisenmenger, VSD	28	F
2	38	F	1.56	60	Lymphangioleiomyomatosis	14	F
3	41	M	1.74	70	Emphysema	23	M
4	21	M	1.67	54	Univentricular heart and pulmonary hypertension	27	M
5	18	M	1.73	60	Complex pulmonary atresia	15	M
6	47	M	1.71	65	Primary pulmonary hypertension	35	F
7	33	M	1.69	60	Emphysema	25	M
8	25	F	1.70	50	Primary pulmonary hypertension	26	M
Mean (SD)	33 (11)		1.68 (0.06)	61 (7)		24 (7)	
<i>Cardiac transplant</i>							
1	51	F	1.65	63	DCM	20	F
2	45	F	1.60	78	Ischaemic heart disease	35	F
3	38	M	1.83	87	DCM	33	M
4	18	M	1.56	42	Complex congenital heart disease	21	F
5	23	M	1.78	69	DCM	17	M
6	51	M	1.73	94	DCM	14	F
7	32	M	1.77	74	DCM	17	F
8	17	F	1.67	48	DCM	24	M
Mean (SD)	34 (14)		1.70 (0.10)	69 (18)		23 (8)	
<i>Controls</i>							
1	45	F	1.68	65			
2	40	F	1.65	57			
3	37	M	1.85	84			
4	21	M	1.68	66			
5	17	M	1.70	65			
6	48	M	1.80	75			
7	30	M	1.60	76			
8	24	F	1.56	49			
Mean (SD)	33 (12)		1.69 (0.10)	67 (11)			

FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; FEV₁% and FVC%, results expressed as percentage of predicted⁵; b neg, no histological evidence of rejection; PCI, patchy cellular infiltrate, no myocytolysis (cyclosporin effect); CYA, cyclosporin; AZA, azathioprine; ASA, aspirin; DYP, dipyridamole; PRED, prednisone; NFD, nifedipine; HYD, hydralazine; MDP, methyldopa; DCM, dilated cardiomyopathy; VSD, ventricular septal defect.

minute until symptom limited maximum exercise. The subjects breathed via a mouthpiece through a Hans Rudolph valve box (Hans Rudolph, Kansas City, USA). Tidal volume, respiratory frequency, and minute ventilation were measured by a turbine ventilation monitor (PK Morgan, Rainham, UK). Mixed expired oxygen and carbon dioxide concentrations were measured by sampling from a mixing chamber by a computer assisted mass spectrometer (Spectralab "M", VG Medical, Middlewich, UK) and used to calculate oxygen consumption and carbon dioxide production.⁶ End tidal carbon dioxide concentrations were measured at the mouth with a catheter probe connected to the mass spectrometer. The presence of a plateau in the expiratory carbon dioxide tracing was confirmed by a chart recorder; the shape of the tracings was similar in the three groups. Arterial oxygen saturation was recorded continuously with a ear oximeter (Biox III Pulse Oximeter, Ohmeda, Harlow, UK).

Blood pressure was recorded with a sphygmomanometer. Twelve lead electrocardiograms were recorded on a Marquette MAC I exercise electrocardiograph system (Marquette, Manchester, UK),

which was also used to measure heart rate. Average values for heart rate and each respiratory variable were measured for each minute. Blood pressure and 12 lead electrocardiograms were recorded at rest and at the end of each three minutes of exercise. The subjects quantified their sensation of breathlessness at the end of each minute on a visual analogue scale.⁷ A hand controlled linear potentiometer, mounted in a convenient position on the handlebars, allowed the patients to indicate their degree of breathlessness by moving a light along a 10 cm linear display, the ends of which were marked "not at all breathless" and "extremely breathless". At the end of the test each person was asked to report the symptoms limiting their exercise capacity.

STATISTICAL ANALYSIS

The baseline characteristics of the three groups were compared by analysis of variance. The results are given as mean (SD). Statistical analysis was performed by Student's *t* test for unpaired data and two way analysis of variance. The level of significance was taken as *p* < 0.05 in a two tailed test. Graphs showing the data subjected to analysis of variance include

V_1 (l)	FEV ₁ %	FVC (l)	FVC %	Time after operation (days)	Biopsy	Drug treatment
<i>Heart-lung transplant</i>						
8	121	3.71	118	319	Neg	CYA, AZA, ASA
3	93	2.75	91	364	Neg	CYA, AZA, ASA, DYP, NFD
4	104	4.21	91	723	Neg	CYA, AZA, DYP, HYD
2	104	4.59	98	449	Neg	CYA, AZA, ASA, DYP
7	87	4.3	84	372	Neg	CYA, ASA, AZA
0	106	4.28	100	366	Neg	CYA, AZA, ASA, DYP
4	121	5.18	114	372	Neg	CYA, AZA, ASA, DYP
5	76	3.08	77	119	Neg	CYA, AZA, ASA, DYP
9 (0.76)	102 (16)	4.01 (0.80)	97 (14)	385 (167)		
<i>Cardiac transplant</i>						
4	99	3.14	109	359	Neg	CYA, AZA, NFD
6	99	2.95	98	261	Neg	CYA, AZA, ASA, PRED
10	100	5.15	99	286	Neg	CYA, AZA, NFD
4	75	3.00	72	251	Neg	CYA, AZA, ASA, DYP, PRED
19	89	4.57	86	356	Neg	CYA, AZA, ASA, DYP, MDP, HYD
1	107	4.67	109	604	Neg	CYA, AZA
17	104	5.51	110	364	PCI	CYA, AZA, ASA, DYP, HYD
18	62	2.27	56	155	Neg	CYA, AZA, ASA, DYP
16 (0.98)	92 (16)	3.91 (1.20)	92 (20)	330 (132)		
<i>Controls</i>						
3	94	3.77	111			
4	118	4.04	120			
2	89	5.14	96			
14	93	4.54	95			
17	87	4.07	81			
37	100	5.72	114			
77	107	4.47	109			
41	115	3.68	108			
59 (0.40)	100 (12)	4.42 (0.71)	104 (13)			

Fisher's least significant difference for comparing observations between groups at the 5% significance level.⁸ The visual analogue scores at maximum exercise were analysed non-parametrically by the Mann-Whitney U test.

Results

There were no significant differences in the baseline characteristics of the three groups (table 1).

BEFORE EXERCISE

All subjects were in sinus rhythm. The controls had normal electrocardiograms. Three patients with heart-lung transplants had electrocardiograms that were within normal limits; one had complete right bundle branch block and four had T wave inversion in the anterior chest leads; one of these four also had T wave inversion in the inferior leads and another had left ventricular hypertrophy on voltage criteria ($SV_2 + RV_5 > 3.5mV$). This subject's blood pressure at rest was 100/70 mm Hg and he was not receiving antihypertensive treatment. Five of the cardiac transplant recipients had electrocardiograms

within normal limits; one had partial right bundle branch block and two had T wave inversion in the anterior chest leads.

MAXIMUM EXERCISE

All subjects were exercised to their symptom limited maximum and no adverse reactions occurred during the test. Table 2 shows the symptoms limiting exercise capacity. Figure 1 shows the maximum level of exercise achieved in the three groups as indicated by workload and oxygen consumption in both transplant groups. The maximum workload was lower than in the normal controls ($p < 0.01$). There was no significant difference between the maximum workload achieved between the cardiac transplant recipients and the heart-lung recipients. Peak oxygen uptake was lower in both transplant groups but the difference only reached statistical significance for the heart-lung group ($p < 0.05$). Peak oxygen uptake in relation to body weight was also lower in the transplant groups: normal controls 30 (4) ml/kg; heart-lung recipients 22 (7) ml/kg ($p < 0.05$), and heart transplant recipients 23 (10) ml/kg ($p = NS$). The normal controls achieved higher maximum heart

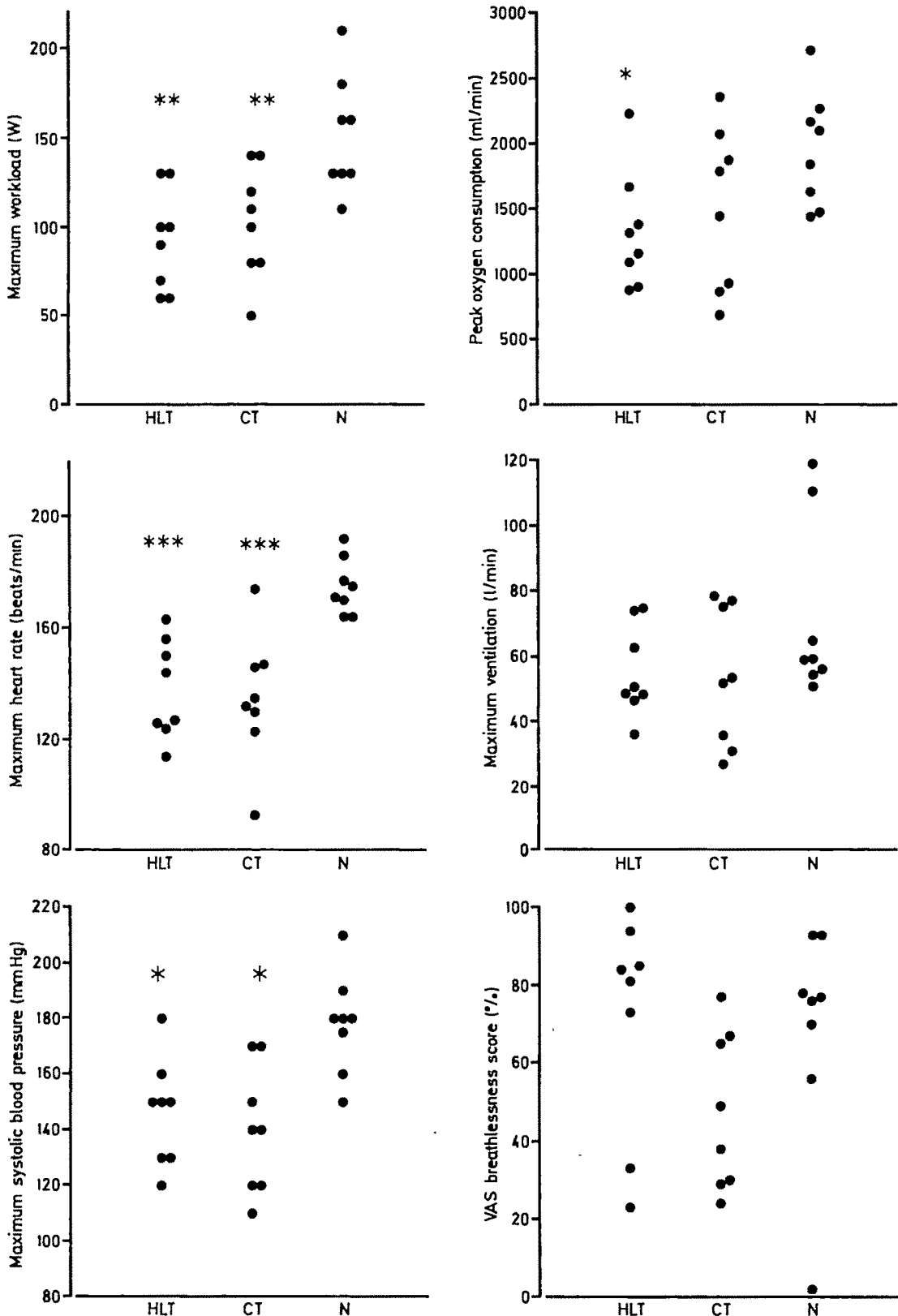


Fig 1 Maximum exercise response in heart-lung transplant recipients (HLT); orthotopic cardiac transplant recipients (CT); normal controls (N). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ for unpaired t tests (comparison with normal controls). VAS, visual analogue scale.

Table 2 Symptoms limiting exercise capacity during test

	Heart-lung transplant	Cardiac transplant	Normal
Fatigue	2	6	6
Dyspnoea	2	1	1
Both	4	1	1

rates than either of the transplant groups ($p < 0.001$).

There was no significant difference in maximum ventilation. Maximum systolic blood pressure was higher in the normal subjects than in either transplant group ($p < 0.05$). There was no significant difference in breathlessness at maximum exercise, as measured by the visual analogue scale, between the normal subjects and either transplant group (Mann-Whitney U test).

PATTERN OF EXERCISE RESPONSE

We examined the differences in the incremental response to exercise in the three groups by a two way analysis of variance. Because this approach required an equal number of data points in each group, the response could be analysed only up to the maximum workload achieved by all subjects (50 W) (fig 2).

Cardiovascular response

All subjects remained in sinus rhythm throughout the test and no significant electrocardiographic changes occurred during exercise. At rest the heart rates of both transplant groups were significantly greater than that in the normal controls ($p < 0.01$). During exercise there were no significant differences in heart rates at workloads where analysis of variance could be performed. To determine the workload at which the heart rate was significantly increased from the resting level, we used Fisher's least significant difference for observations within a group (for $p < 0.05$).⁸ In the normal subjects this occurred at the first stage of exercise (10 W) whereas in both transplant groups it did not occur until the 30 W stage (that is the response was delayed by two minutes). There was no significant electrocardiographic changes during exercise in any subject.

Figure 2 shows the blood pressure response of the three groups. There were no significant differences in systolic blood pressure between the three groups at rest, 30, or 60 W (one cardiac transplant recipient did not reach the 60 W stage and the blood pressure at 50 W was used for analysis of variance). Systolic blood pressure rose significantly on exercise in all three groups ($p < 0.001$). Heart-lung recipients tended to have slightly lower diastolic pressures and this difference was just significant at the 30 W stage. There was no significant change in diastolic blood pressure in any group during exercise.

Respiratory response

Before exercise the heart-lung transplant group tended to have higher values for ventilation, oxygen uptake, and carbon dioxide production; however, the difference was statistically significant only for carbon dioxide production during the first minute. During exercise there was no significant difference in oxygen consumption or carbon dioxide production among the three groups. Ventilation was greater in the heart-lung transplant recipients than in the normal controls and this was statistically significant at and above the 30 W stage. Ventilation in the cardiac transplant patients was, in general, higher than that in the normal controls but this difference was only significant at the 30 W stage. The increase in ventilation in the heart-lung transplant patients was achieved by an increase in both tidal volume and respiratory rate while that in the cardiac transplant patients was achieved by an increase in respiratory rate alone.

The oxygen consumption corresponding to the anaerobic threshold for each subject was estimated from the point where ventilation began to increase non-linearly with oxygen uptake.⁹ For the normal subjects this was 1.43 (0.38) l/min oxygen; for the heart-lung group it was 1.0 (0.32) l/min ($p = \text{NS}$), and for the cardiac transplant group it was 1.2 (0.46) l/min ($p = \text{NS}$). The ventilatory equivalent for oxygen in each person was obtained from the slope of the linear regression line of ventilation against oxygen uptake below the anaerobic threshold.¹⁰ The mean slope for the normal controls was 23.9 (5.5); for the heart-lung group it was 30.8 (6.1) ($p < 0.05$), and for the cardiac transplant group it was 25.8 (3.2) ($p = \text{NS}$). The ventilatory equivalent for carbon dioxide was obtained in a similar manner. The mean slope for the normal controls was 23.5 (3.2); for the heart-lung group it was 30.5 (4.7) ($p < 0.01$), and for the cardiac transplant group it was 27.1 (3.8) ($p = \text{NS}$).

Oxygen saturations were similar for all three groups. The end tidal carbon dioxide value was significantly lower in the heart-lung recipients than in the normal ($p < 0.02$) and cardiac transplant ($p < 0.02$) groups.

Discussion

Combined heart-lung transplantation can alleviate symptoms and improve the quality of life of patients with severe pulmonary vascular disease and parenchymal lung disease.³ We have been impressed by the excellent degree of rehabilitation achieved by most heart-lung transplant recipients. In some patients, however, long term complications develop (especially chronic airflow obstruction in the transplanted lung¹¹), and the physiological consequences

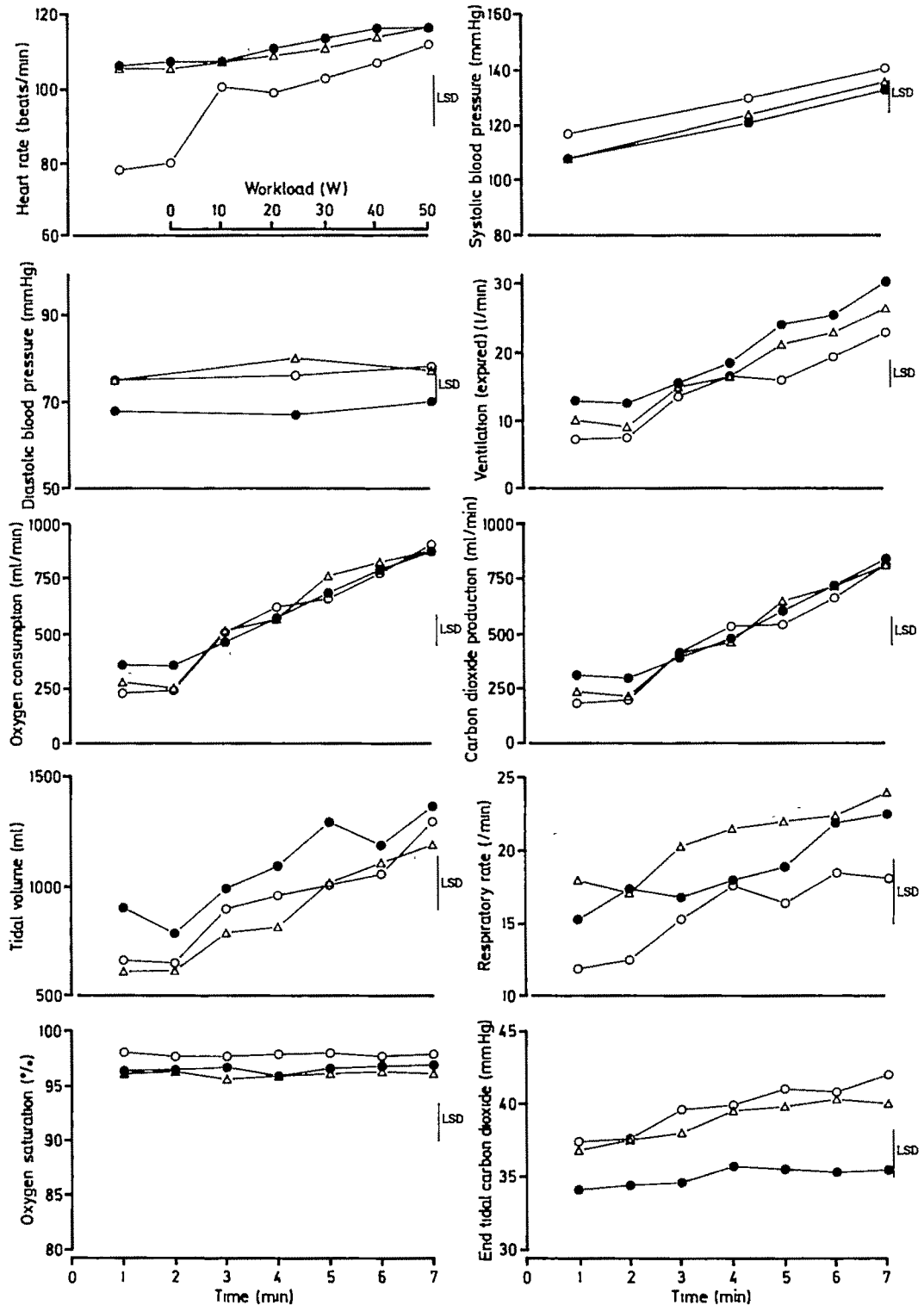


Fig 2 Evolution of the exercise response in heart-lung transplant recipients (●), cardiac transplant recipients (Δ), and normal controls (○). LSD, Fisher's least significant difference for observations between groups ($p < 0.05$).

of the procedure have not been fully defined. This study was designed to compare the exercise capacity and pattern of exercise response of a group of healthy heart-lung transplant recipients with those of cardiac transplant recipients and normal controls. We selected transplant recipients who had no serious complications after transplantation.

Our results confirm the findings of a previous study which showed that recipients of heart-lung transplants had an exercise capacity that was less than that predicted for normal controls.⁴ In addition, we have established that their exercise capacity is similar to that of matched cardiac transplant recipients. The reduced exercise capacity of patients with orthotopic cardiac transplants has already been shown.^{12,13} Several factors may contribute to the reduced exercise capacity after heart and heart-lung transplantation.

Illness before transplantation will have produced a period of deconditioning and muscle wasting that may persist after operation. A recent study showed a delayed recovery in the vasodilator response of skeletal muscle after cardiac transplantation. This may reflect a persistent effect of preoperative cardiac failure and deconditioning, which could affect exercise capacity.¹⁴ A previous study of cardiac transplant recipients at our hospital found them to have a reduced lean body mass and exercise capacity compared with normal controls. A programme of regular exercise training improved exercise capacity and increased lean body mass although their exercise capacity was still less than that of controls.¹⁵

There is the possibility of residual left ventricular dysfunction related to the process of brain death in the donor,¹⁵ the organ preservation at the time of transplantation, and subsequent episodes of cardiac rejection. We found that the systolic ventricular function of cardiac transplant recipients treated with cyclosporin was, however, usually normal.¹⁶

The heart-lung transplant operation¹⁷ has several physiological consequences. The heart and lungs are transplanted as a single block replacing the recipient's diseased organs. Vascular anastomoses are made between the donor right atrium and a remnant of the recipient's right atrium and between donor and recipient ascending aorta (the donor left atrium remains intact). The tracheal anastomosis is made between the lower part of the recipient's trachea and the donor trachea just above the carina. The procedure results in acute denervation of the transplanted heart and lungs. The recipient retains tracheal innervation down to the level of this anastomosis and the recurrent laryngeal nerves remain intact. The pulmonary lymphatic system and bronchial circulation are sacrificed.

Orthotopic cardiac transplantation results in com-

plete denervation of the transplanted heart but the pulmonary innervation, lymphatic system, and the bronchial circulation are not affected. Cardiac reinnervation has not been seen in patients after orthotopic cardiac transplantation¹⁸ although evidence of efferent reinnervation has been found in recipients at heterotopic transplants.¹⁹ In dogs cardiac and pulmonary reinnervation can occur after transplantation of the heart²⁰ or lung.²¹ The sinus tachycardia before exercise together with the identical, abnormal, heart rate response during exercise of the heart-lung and heart transplant recipients studied here provide evidence of persistent cardiac denervation. It has been difficult to show pulmonary denervation in heart-lung transplant recipients non-invasively because of the presence of an innervated trachea. Recipients of heart-lung transplants do not have an increased cough threshold when tested with a citric acid aerosol (Banner N R *et al*, unpublished). They do, however, have increased airways responsiveness to methacholine. This may represent a denervation hypersensitivity of muscarinic receptors in the airways of the transplanted lung.^{22,23}

The difference in exercise capacity between the transplant groups and normal individuals was not caused by altered mechanical or metabolic efficiency as the relation of oxygen consumption and carbon dioxide production to workload was the same in all three groups. Because the two transplant groups showed a similar performance the overall limitation is likely to be related to the circulation and the transplanted heart rather than to the transplanted lungs. This view is supported by the ventilatory response, which provided indirect evidence of anaerobic metabolism developing during exercise in all three groups in this study, and the increased lactate concentrations found in recipients of heart-lung transplants at maximum exercise in another study.⁴

The abnormal response of heart rate to exercise may contribute to the reduced exercise capacity of the transplant recipient. The increased resting heart rate in the transplant recipients is caused by a loss of vagal tone.¹⁸ The delayed response of heart rate at the start of exercise is associated with an impaired initial cardiac output response.²⁴ All three groups, however, had similar heart rates during the first few minutes of exercise in this study. The lower peak heart rates achieved by the transplant recipients might limit maximum cardiac output or they may just reflect the lower workloads reached by the transplant recipients. The cardiac output of heart transplant recipients (measured under steady state conditions during submaximal exercise) is normal in relation to oxygen uptake.²⁵ The slow response of heart rate may place the transplant patient at a particular disadvan-

tage during an incremental exercise test. A previous study found that the cardiac output response of recipients of heart transplants to exercise was caused by a prominent rise in stroke volume and a slow rise in heart rate; because cardiac output was low in relation to oxygen uptake there was an increase in the arteriovenous oxygen difference.²⁶ Exercise training improves the response of heart rate to exercise in cardiac transplant recipients and the improvement is associated with an increased exercise capacity.¹³ Cardiac denervation may affect cardiac function in other ways. Contractility and the contractile reserve of the left ventricle in the transplanted heart seem normal when tested pharmacologically²⁷ but the effects of chronic cardiac denervation on left ventricular performance during exercise are unknown.

Hypertension is a common complication of cyclosporin treatment in heart transplant recipients.^{28,29} Four heart and two heart-lung recipients in this study were on antihypertensive treatment. The systolic blood pressure response to exercise was similar in all three groups.

Cardiac transplant recipients have been reported to have increased ventilation in relation to oxygen uptake during exercise.¹² The cardiac transplant group in the present study had a slightly increased ventilation compared with the normal controls but the difference was not statistically significant. Analysis by linear regression of ventilation against oxygen uptake shows that the response was close to the published values for a similar exercise protocol.¹⁰ The end tidal carbon dioxide concentrations were normal in the cardiac transplant group, confirming that alveolar ventilation was normal. The relatively normal ventilatory response in these patients may be because of the improvement in ventricular function that we saw in cardiac transplant recipients treated with cyclosporin compared with conventional immunosuppression.¹⁶ In addition, the ventilatory response of cardiac transplant recipients is related to their physical fitness and can be altered by exercise training.¹³

In contrast, both analysis of variance at equivalent workloads or by linear regression of ventilation against oxygen below the anaerobic threshold showed an increased ventilatory response in the heart-lung group; this was owing to a combination of increased respiratory rate and tidal volume. A case of increased ventilation during exercise in a heart-lung transplant recipient was reported while the present work was in progress.³⁰

The increased ventilatory response in our study did not seem to be the result of poor pulmonary gas exchange. Oximetry showed that the heart-lung group did not desaturate during exercise and end tidal carbon dioxide concentrations were low, sug-

gesting that true alveolar hyperventilation was occurring. It may be that the increased ventilation and low end tidal carbon dioxide concentrations were the result of regions of high ventilation and low perfusion in the transplanted lungs. The heart-lung group had good baseline lung function, however, which makes this explanation unlikely. Another study found low arterial carbon dioxide tensions in heart-lung transplant recipients before and during exercise although it did not compare them with those in normal controls.⁴ The alveolar hyperventilation might be caused by the sluggish heart rate response with the early development of a lactic acidosis during exercise. The small increase in ventilation seen in the cardiac transplant group who had a similar exercise capacity and cardiovascular response to exercise does not support this idea. Drug treatment was similar in the two transplant groups so the increased ventilation is not the result of medication.

The mechanisms controlling exercise hyperpnoea are complex and poorly understood. Most of the attention in this area has been focused on mechanisms stimulating ventilation rather than those restraining it.³¹ Our results suggest that an increased ventilatory response to exercise occurs after pulmonary denervation, but not after cardiac denervation. We found that the ventilatory response to carbon dioxide was increased in heart-lung transplant recipients.³² A possible explanation is that the increased ventilatory response to these stimuli is caused by the loss of negative feedback from pulmonary afferents in the heart-lung recipients.

The heart-lung recipients were still able to perceive breathlessness during exercise and the maximum breathlessness scores were similar in the three groups. This indicates that pulmonary afferents do not make an essential contribution to the sensation of exertional dyspnoea.

In conclusion, heart-lung and heart transplant recipients have a similar exercise capacity and cardiovascular response to exercise. The altered cardiovascular response is partly the result of cardiac denervation and their exercise capacity seemed to be limited by circulatory performance. The heart-lung transplant recipients also show an increased ventilatory response during submaximal exercise, which may be caused by a loss of negative feedback from the pulmonary afferents. Exercise capacity after heart-lung transplantation is sufficient for everyday activities and transplantation can provide excellent rehabilitation of patients with end stage cardiopulmonary disease.

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Isometric exercise in the denervated heart: a Doppler echocardiographic study

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SUMMARY The haemodynamic responses to isometric exercise of eight recipients of orthotopic heart transplants and eight healthy controls were studied. Each performed sustained exercise at 30% of maximal voluntary contraction for three minutes on a handgrip dynamometer. Cardiac output was measured by combined Doppler and cross sectional echocardiography before exercise and every 30 seconds during and after exercise. In the controls cardiac output and blood pressure increased significantly owing to an increase in heart rate with no change in stroke volume. In the transplant group cardiac output, heart rate, and stroke volume remained unchanged throughout exercise.

In contrast with its response to dynamic exercise the denervated human heart is unable to increase cardiac output during isometric exercise. The pressor response that occurs is mediated via an increase in peripheral vascular resistance.

Although reinnervation of the transplanted heart has been well documented after orthotopic transplantation of the canine heart,¹ the transplanted human heart seems to remain both functionally and anatomically denervated indefinitely.² Studies in normally innervated human hearts have shown that isometric exercise results in significant increases in cardiac output, heart rate, and mean blood pressure without changes in stroke volume, ventricular dimensions, or myocardial contractility.³⁻⁵ Although the transplanted denervated heart is able to maintain a relatively normal cardiac output during dynamic exercise⁶⁻⁸ through the Frank-Starling mechanism, it is difficult to envisage how it can produce an appropriate increase in cardiac output during semi-supine static exercise.

Cardiac output can be calculated from blood velocity in the ascending aorta, measured by Doppler ultrasound, combined with aortic orifice area, measured by cross sectional echocardiography.^{9,10} The technique is reproducible^{11,12} and allows quick, non-invasive measurements of cardiac output both at rest and during supine and upright exercise.¹³⁻¹⁵ Left ventricular size and performance can be accurately

measured by M mode echocardiography.^{16,17} We used these techniques to investigate the haemodynamic changes during handgrip isometric exercise in recipients of orthotopic heart transplants and in controls.

Patients and methods

Eight recipients of orthotopic heart transplants (six men) were recruited. The details of the group were as follows: mean (SD) age 40 (10) years, mean (SD) height 1.71 (0.08) m, mean (SD) weight 64.8 (9.5) kg. All patients were clinically and functionally well with no clinically significant biochemical or haematological abnormality at the time of the study. Mean haemoglobin was 12.3 g/l and mean creatinine clearance was 58 ml/min. The mean length of survival after transplantation was 11 (range 5-21) months and all patients were receiving standard immunosuppressive treatment (prednisolone, azathioprine, and cyclosporin). In all cases a recent cardiac biopsy specimen had shown no evidence of rejection. We also studied eight normal healthy volunteers (seven men), who were age and sex matched to the heart donors (mean age 25 (6) years, mean height 1.76 (0.08) m, mean weight 68.0 (8.8) kg).

All those studied were known to be good echocardiographic subjects. The experimental protocol was approved by the ethical committee of Newcastle Health Authority. The procedure was explained to

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each person and their informed consent was obtained.

Investigations were performed in a warm quiet room with the subjects in the semisupine position after they had rested for 10 minutes. Basal measurements were recorded on two occasions, five minutes apart, and the mean value was taken as the baseline. They performed isometric exercise on a Harpenden handgrip dynamometer (British Indicators). Participants were asked to exert the maximal compressive force with their dominant hand on three occasions to determine maximal voluntary contraction. After a further 10 minutes' rest they were asked to perform isometric exercise at 30% of their maximal voluntary contraction for three minutes. Investigations were repeated after 30, 60, 90, 120, and 180 seconds of exercise and then 1, 3, 5, and 10 minutes after exercise. The participants were carefully observed to ensure that none of them performed the Valsalva manoeuvre during the exercise period.

The Doppler principle and the assumptions of the Doppler method for calculation of cardiac output have been described elsewhere.¹⁸ Aortic velocities were recorded by a 1.9 MHz independent continuous wave Doppler transducer (Hewlett-Packard 77020A). Cross sectional and M mode echocardiograms were recorded by a 3.5 MHz transducer (ATL Mark 4). Doppler velocities and M mode echocardiograms were recorded, along with an electrocardiogram, on a strip chart at a paper speed of 100 mm/s. Blood pressure was measured from the non-exercising arm by an automatic sphygmomanometer (Dynamap).

Blood velocity in the ascending aorta was recorded from the suprasternal notch by continuous wave Doppler. The direction of the ultrasound beam was adjusted until the highest velocities with the "cleanest" envelope were obtained and then 10–15 cardiac cycles were recorded. These velocities were taken to represent velocities at the aortic orifice with the ultrasound beam parallel with flow. The area under the velocity curve or velocity integral (VI) was determined by tracing from the baseline around the maximum velocity curve with a digitising tablet linked to a microcomputer.¹⁹ Eight to 10 beats were averaged for each determination.

The aortic diameter was measured from cross sectional echocardiograms recorded on videotape. The orifice diameter was measured during systole from the parasternal long axis plane by the leading edge to leading edge method. The diameters from five consecutive beats were averaged and the cross sectional area (CSA) was calculated from the equation $\pi \times (D/2)^2$ where D = mean aortic diameter. Simultaneous cross sectional and Doppler echocar-

diographic recordings were made at each time point. Heart rate (HR) was determined directly from the RR interval of the simultaneously recorded electrocardiograph. Stroke volume (SV) and cardiac output (CO) were calculated as follows:

$$SV \text{ (ml)} = VI \text{ (cm)} \times CSA \text{ (cm}^2\text{)}$$

$$CO \text{ (l/min)} = SV \text{ (ml)} \times HR \text{ (min}^{-1}\text{)} - 1000.$$

Standard left ventricular M mode echocardiograms were recorded from the parasternal long axis plane.²⁰ Left ventricular end diastolic dimension (EDD) and end systolic dimension (ESD) were obtained from the tracings according to the recommendations of the joint International Society and Federation of Cardiology/World Health Organisation task force.²¹ Four consecutive beats were averaged for each measurement. Two indices of left ventricular function were calculated from the mean left ventricular measurements. Ejection fraction (EF) was calculated by the following formula:²²

$$EF (\%) = [(EDD)^3 - (ESD)^3] \div (EDD)^3$$

The mean velocity of circumferential fibre shortening (mean Vcf) was calculated from the following formula:²³

$$\text{Mean Vcf (diameters/s)} = (EDD - ESD) \div (\text{ejection time} \times EDD)$$

The left ventricular ejection time was determined from the aortic velocity trace.

STATISTICAL ANALYSIS

A repeated measures analysis of variance was performed for each variable with the *Biomedical Programs Statistical Package* (BMDP). The total variance consists of a component to take account of differences between the subjects (σ_s^2) and a component for differences within subjects (σ_w^2). The within subject variance is made up of a component for differences between time points (σ_t^2) and a component representing the residual variability (σ_r^2).

To make allowance for the problem of multiple significance testing, the differences between time points within the transplant and control groups were compared by means of the studentised range at the 1% level²⁴ (studentised range = $q(v) \times [\sigma_r - \sqrt{n}]$, where $q(v)$ = critical value for comparing two time points, σ_r^2 = residual mean square with v degrees of freedom, and n = number of subjects). Thus any change greater than the studentised range was considered to be statistically significant. Comparisons between the transplant and control groups at each time were based on approximate 95% confidence intervals for each variable:

$$\text{Mean} \pm 2 \times \sqrt{[\sigma_s^2 + \sigma_r^2] \pm 8}.$$

Results

The mean (SD) value for 30% of the maximal voluntary contraction was 10.0 (1.6) kg in the transplant group and 14.2 (2.7) kg in the control group

($p < 0.002$). Two transplant recipients could only maintain 30% of their maximal voluntary contraction for approximately 150 s, so data after 180 s exercise was only available for six in this group. Satisfactory serial echocardiographic recordings

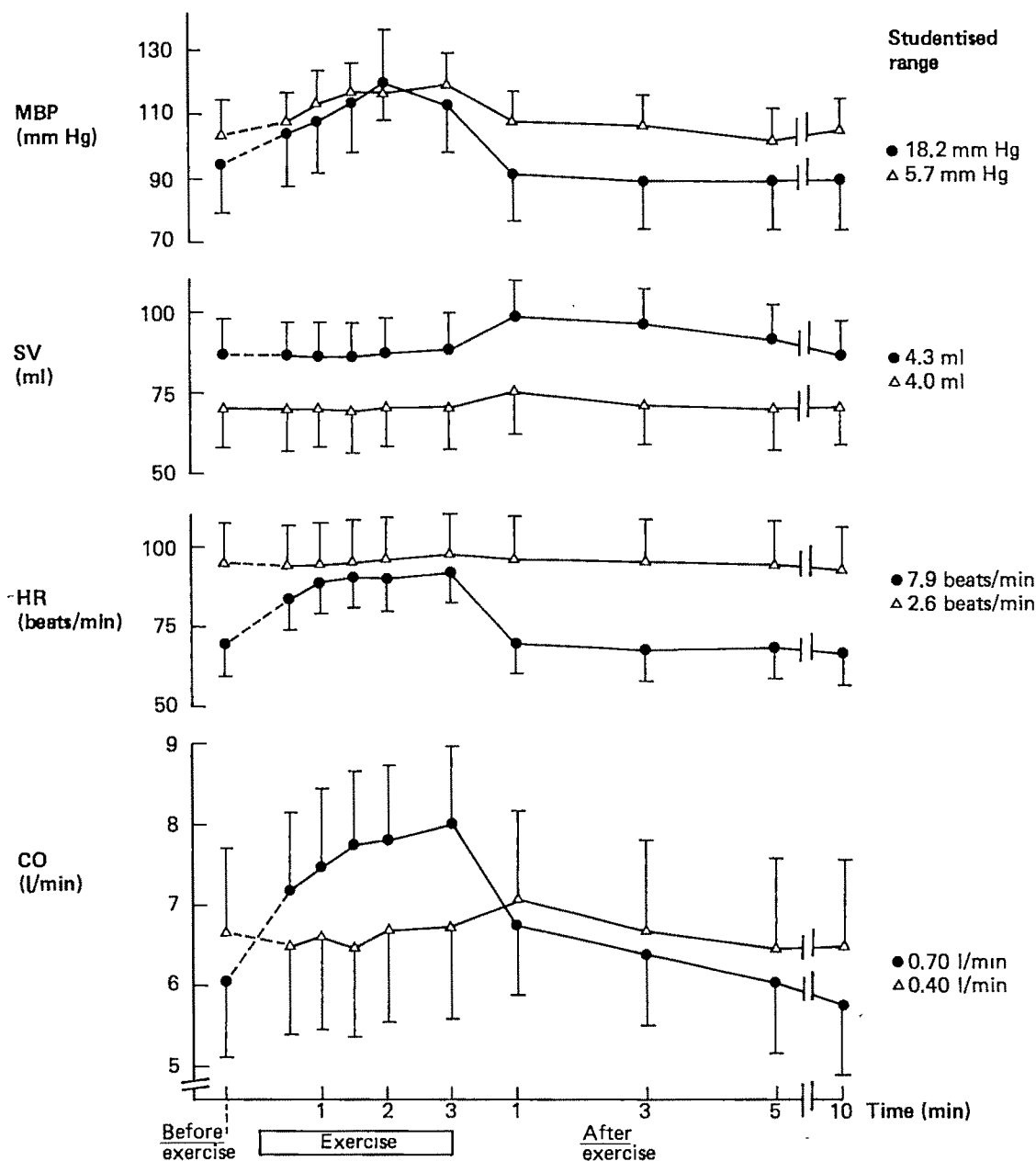


Fig 1 Changes in mean blood pressure (MBP), stroke volume (SV), heart rate (HR), and cardiac output (CO) during and after isometric exercise in heart transplant recipients (Δ) and controls (●). Values shown are means and 95% confidence intervals. The studentised ranges for the two groups are shown on the right (see text for explanation).

were obtained from all time points in the remainder. Figure 1 shows changes in mean blood pressure, heart rate, stroke volume, and cardiac output. Figure 2 shows changes in left ventricular end diastolic and end systolic dimensions, ejection fraction, and mean

rate of circumferential fibre shortening (mean Vcf).

CONTROL GROUP

Mean blood pressure increased from 94.8 mm Hg before exercise to 113.8 mm Hg at the end of

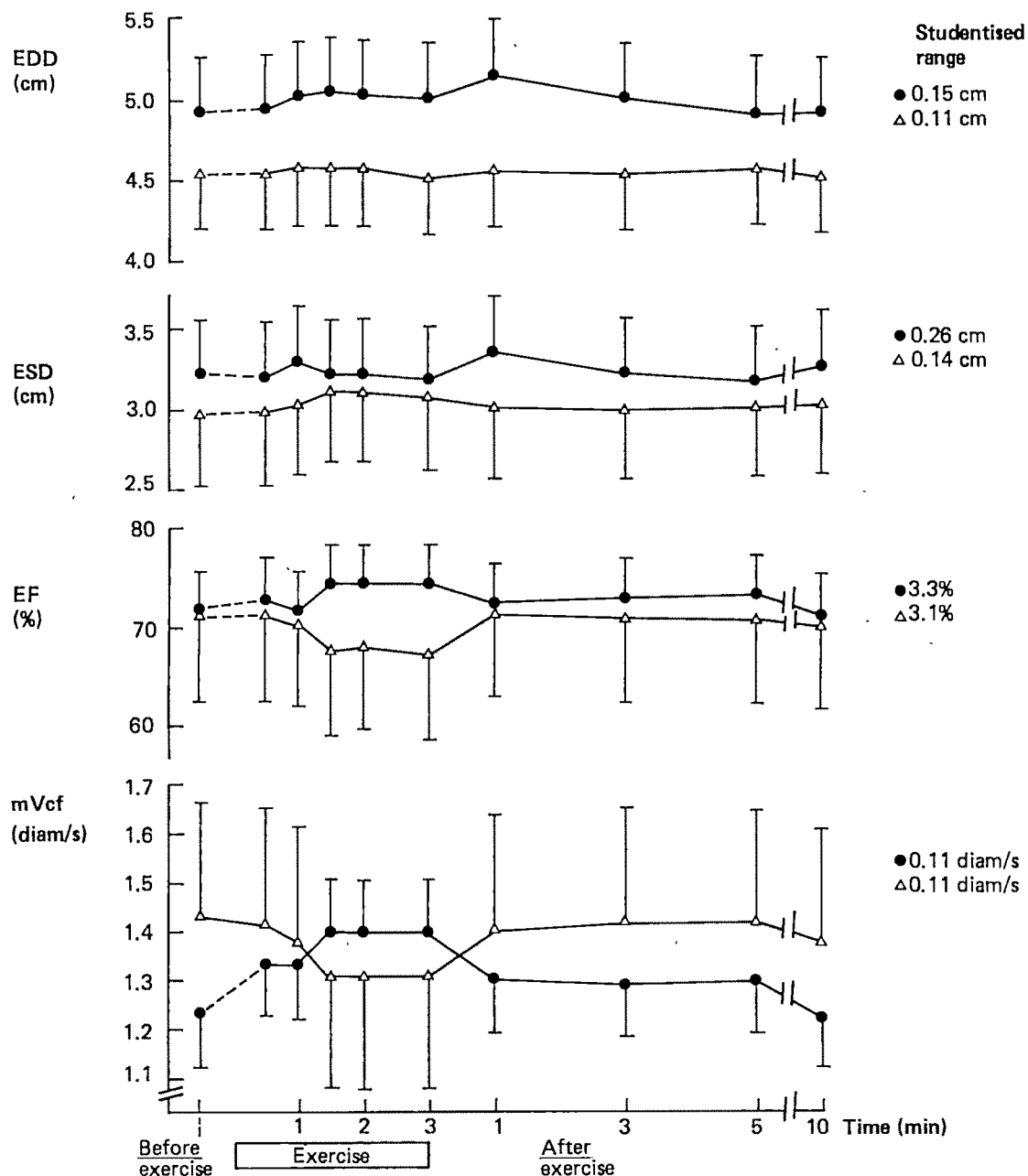


Fig 2 Changes in left ventricular end diastolic dimension (EDD), end systolic dimension (ESD), ejection fraction (EF), and mean rate of circumferential fibre shortening (mVcf) during and after isometric exercise in heart transplant recipients (Δ) and controls ($\bullet$). Values shown are means and 95% confidence intervals. The studentised ranges for the two groups are shown on the right (see text for explanation).

exercise, the increase being significant by 1.5 minutes of exercise. Blood pressure had returned to pre-exercise values within one minute of the end of exercise. Stroke volume before exercise was 87.0 ml and there was no change during exercise. One minute after the end of exercise, however, stroke volume increased to 98.4 ml and was still higher than pre-exercise values three minutes after the end of exercise. Mean heart rate before exercise was 70.0 beats/min and increased to 84.2 beats/min within 30 seconds of the start of exercise, reaching a maximum after three minutes' exercise (92.0 beats/min). Heart rate also returned to pre-exercise values within one minute of the end of exercise. Cardiac output increased from a mean of 6.05 l/min before exercise to a maximum of 8.07 l/min after three minutes' exercise, the increase being significant after one minute. Immediately after exercise stopped cardiac output fell to 6.80 l/min but this was still higher than before exercise, and basal values were not reached till three minutes after exercise.

The end diastolic left ventricular dimension was larger one minute after exercise (5.18 cm) than before exercise (4.93 cm) or after three minutes' exercise (5.02 cm). The end systolic dimension and ejection fraction did not change significantly during the study. Although mean velocity of circumferential fibre shortening increased during exercise from 1.23 diameters/second before exercise to 1.40 at three minutes, this primarily reflects the increase in heart rate. When mean velocity of circumferential fibre shortening was standardised for heart rate according to the formula of Mangiarotti *et al*²⁵ there was no longer a significant increase. Thus there was no evidence of a change in myocardial contractility, independent of heart rate, during isometric exercise in the control group.

TRANSPLANT GROUP

Mean blood pressure increased from 105.0 mm Hg before exercise to 120.6 mm Hg after three minutes of exercise, the increase being significant after one minute. Blood pressure returned to basal values within one minute of the end of exercise. As in the control group, stroke volume remained constant during exercise but increased one minute after it had stopped, from 69.3 ml at the end of exercise to 74.5 ml. Although stroke volume was consistently lower in the transplant group than in the controls this variable only reached significance at one and three minutes after exercise. The resting heart rate before exercise was 95.6 beats/min, which was significantly higher than the resting heart rate in the control group. There was no change in heart rate during or after exercise. The mean cardiac output before exercise (6.66 l/min) was not significantly different

from that found in the control group. In contrast with the controls, however, there was no change in cardiac output during exercise. One minute after the end of exercise cardiac output increased to 7.08 l/min but had returned to basal values by three minutes after the end of exercise.

The end diastolic dimension remained unchanged during the period of study. The end systolic dimension increased from 2.97 cm before exercise to 3.14 cm after 1.5 minutes of exercise. This increase was maintained until the end of exercise, returning to pre-exercise values by 1 minute after the end of exercise. The ejection phase indices showed a rather different pattern in the transplant recipients. Both ejection fraction and mean velocity of circumferential fibre shortening decreased during exercise. Analysis of the changes in individual subjects found four who showed a pronounced fall in both ejection phase indices; the remainder showed little change.

Discussion

The assessment of ventricular performance by Doppler echocardiography is now well established. It has been validated in both resting^{9,10} and exercising subjects.^{13,14} This study is the first to use this reliable, non-invasive, repeatable method to look at the response to isometric exercise of the denervated heart.

We showed that during sustained handgrip exercise in normal people there is a statistically significant increase in blood pressure, heart rate, and cardiac output. Left ventricular dimensions, stroke volume, and ejection fraction are unchanged and mean rate of circumferential fibre shortening when corrected for the increase in heart rate is also unchanged. The haemodynamic effects of isometric exercise in healthy adults by various techniques and our results accord with these studies.²⁶⁻²⁸

In controls the pronounced increase in blood pressure was primarily caused by an increase in cardiac output with no significant change in the calculated systemic vascular resistance. As we have shown, this increased cardiac output was predominantly the result of an increase in heart rate with no change in stroke volume. End diastolic volume and pressure, determinants of preload, and end systolic dimension (which is relatively preload independent) were unchanged. Despite the ventricular geometry remaining constant during the period of exercise, blood pressure increased.

In this study the transplant patients showed a near normal pressor response but there were no significant changes in heart rate or cardiac output during exercise. End diastolic and end systolic dimensions and stroke volume were unchanged during the period

of exercise, as in the normal group. This is in marked contrast with the situation during dynamic exercise in such patients when, the initial response, at least, is caused by increased venous return and an increase in cardiac output via the Frank-Starling mechanism.⁷ The only other study to look at the response of denervated hearts to isometric exercise is by Savin *et al.*²⁹ They used an invasive technique and compared patients with denervated hearts with patients undergoing cardiac surgery rather than with healthy controls. Wire coils were implanted in the left ventricle at the operation and data were obtained by fluoroscopy only once before and once after sustained handgrip exercise. The responses of the innervated hearts in their study were at variance with most other studies and they concluded that in both innervated and denervated hearts the response to isometric exercise results from an increase in systemic vascular resistance.

During sustained handgrip exercise, if preload and heart rate are unchanged, the rapid near normal pressor response we have shown is likely to be the result of an increase in systemic vascular resistance. We suggest that during isometric exercise in transplant patients afferents from the exercising muscles are stimulated as in normal individuals and, although the heart is denervated and unable to respond directly, the efferent pathways to peripheral arterioles remain intact and respond to sympathetic stimulation. This leads to vasoconstriction and an increase in systemic vascular resistance and an increase in blood pressure.

The tendency of the mean velocity of circumferential fibre shortening and ejection fraction to fall during the period of exercise in the transplant patients was the result of a considerable reduction in four of the eight patients. This reduction in these four patients may reflect impaired left ventricular reserve and increasing difficulty in pumping against an increasing afterload. This reduction is also seen in normal people during very strenuous exercise and in patients with coronary artery disease.³⁰ This tendency of the rate of circumferential fibre shortening to fall in some patients requires further investigation.

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Exercise testing soon after myocardial infarction: its relation to course and outcome at one year in patients aged less than 55 years

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SUMMARY A consecutive series of 184 patients aged < 55 years who had an acute myocardial infarction were enrolled in a study to examine outcome at one year. One hundred of these patients underwent a maximal exercise test six weeks after infarction to evaluate its ability to predict cardiac events. The in-hospital mortality for the series was 7.6% (14 deaths) and the one year mortality for the 170 survivors was 3.8% (seven deaths). During the exercise test 31 patients had angina and 21 had ST depression. During the one year follow up period 39 of 100 patients had angina on exertion, 15 patients underwent coronary artery surgery, three patients had a reinfarction, and one patient died. Angina during the exercise test but not ST segment depression during the exercise test predicted angina on exertion and the need for coronary artery surgery. In the year of follow up angina occurred during everyday exertion in 25 (81%) (95% confidence interval 62 to 92%) of the 31 patients who developed angina during the exercise test and in only 14 (20%) (95% confidence interval 12 to 32%) of 69 patients who did not, and coronary artery surgery was performed in 11 (35%) (95% confidence interval 19 to 54%) of the 31 patients with angina during the exercise test and only four (6%) (95% confidence interval 2 to 15%) of 69 patients without angina.

The outcome after myocardial infarction in patients aged < 55 years was good and the occurrence of angina, but not ST segment depression, during a maximal exercise test six weeks after infarction was an indication for further investigation.

The aims of management in younger survivors of acute myocardial infarction include full rehabilitation of the patients so that they can return to normal lives and, if possible, a reduction in subsequent morbidity and mortality. To achieve this those patients who are at increased risk of death, reinfarction, and other cardiac events must be identified. This requires a reliable and preferably non-invasive method of predicting important cardiac events and of selecting patients who may benefit from further investigation. There have been several studies to assess the value of exercise testing soon after infarction.¹⁻³ Unfortunately most included substantial numbers of elderly patients (over 60 years^{1,3} and even up to 79 years²) and presented no information specific

to younger patients, despite strong evidence of the independent effect of age on outcome in survivors of acute myocardial infarction.⁴⁻⁶ This study was therefore designed to determine the outcome and value of a symptom limited exercise test six weeks after infarction in predicting cardiac events during the first year after infarction in a consecutive group of patients aged < 55.

Patients and methods

STUDY POPULATION

The study population was drawn from 184 consecutive patients under the age of 55 years admitted to our coronary care unit between October 1981 and February 1984 with confirmed acute myocardial infarction. The diagnosis of acute myocardial infarction was based on the presence of the following: (a) a history of typical chest pain lasting at least 30 minutes and (b) a rise in the activity of cardiac enzymes (creatinine kinase, lactic dehydrogenase, or

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aspartate aminotransferase) to at least twice the upper limit of normal or (c) characteristic electrocardiographic changes—that is a sequential rise of ST segment, inversion of T waves, and appearance of new Q waves.

Fourteen (7.6%) patients died in hospital. Seventy patients were excluded from the study for various reasons. Three could not be exercised because of left ventricular failure and nine because of limiting neurological or orthopaedic disease. Thirteen patients were excluded because of severe non-cardiac disease and 22 patients refused to take part in the study. Six patients lived too far away for adequate follow up, and 17 patients were excluded for various administrative reasons.

So we studied 100 survivors of an acute myocardial infarction under the age of 55 years (10 women and 90 men; mean age 46.6 years (range 32–54)). Five patients had a history of previous myocardial infarction and four were taking β blockers at entry into the study.

EXERCISE TESTING

All patients had a symptom limited treadmill exercise test during a modified Bruce protocol (table) six weeks after infarction (range 35–50 days, mean 42.7 days). Exercise was stopped if: (a) the patient developed limiting symptoms of chest pain, dyspnoea, or fatigue; (b) there was a sustained fall in systolic blood pressure of ≥ 20 mm Hg from values attained earlier during exercise; (c) ventricular extrasystoles occurred in runs of three or more; or (d) there was ST segment depression of ≥ 4 mm.

Throughout the exercise test leads II, V2, and V5 were monitored continuously. Blood pressure and standard 12 lead electrocardiograms were recorded every three minutes during exercise and at 1, 3, and 5 minutes after exercise or until the electrocardiogram was normal and the patient was comfortable, whichever was longer. We analysed the following exercise test variables: (a) the development of angina, (b) significant ST depression defined as at least 1 mm horizontal or downsloping ST segment depression measured 0.08 s from the J point of the QRS complex, and (c) the duration of exercise.

CORONARY ARTERIOGRAPHY

All patients had a coronary arteriogram and left ventricular angiogram at a mean of three months after infarction. The left ventricular angiograms were recorded in both the 30° right anterior oblique and either 60° left anterior oblique or lateral projections. At least two orthogonal views of each coronary artery were obtained. Clinically significant coronary artery stenosis was defined as at least a 70% reduction in intraluminal diameter. Each angiogram was repor-

ted independently by two observers and differences of opinion were settled by consensus. Left ventricular ejection fractions were calculated from the 30° right anterior oblique angiogram by the area-length method for single plane angiograms.⁷ There were no complications associated with angiography or exercise testing.

FOLLOW UP

All patients, including those excluded from exercise testing, were followed up as outpatients. The frequency of review depended on their progress and severity of symptoms. A full, formal clinical assessment of all patients was undertaken at one year. The events of interest were death, reinfarction defined by the same criteria for infarction as for entry into the study, coronary artery surgery, and the development of stable or unstable angina pectoris. Coronary artery surgery was recommended for two patients with severe left main stem lesions but was only advised because of symptoms in the other patients.

STATISTICAL ANALYSIS

Exercise test variables were examined in relation to the selected end points. The χ^2 test with Yates' correction for small numbers and Fisher's exact test were applied as appropriate. Values of $p < 0.05$ were considered to be significant. Proportions are presented with their 95% confidence intervals (CI). The mortality rates in the exercised patients and in those excluded from exercise testing were compared by calculating a standardised mortality ratio for the two groups. This relates the mortality rate within each of the groups to the expected mortality rate of an age and sex matched group of the general population and is expressed as a percentage $\pm$ standard error.

Results

EXERCISE TEST END POINTS

The exercise test was terminated because of angina in 31 patients, exhaustion in 67 patients, and a fall in systolic blood pressure in two patients. Neither the extent of ST segment depression nor the occurrence of ventricular arrhythmias was an end point to any of the exercise tests.

CORONARY ANATOMY

Twelve patients had three vessel disease, 36 had two vessel disease, and 47 single vessel disease. Five patients had no significant coronary artery disease.

During follow up exertional angina occurred in 39 patients: five (42%) of the 12 patients with three vessel disease, 19 (53%) of the 36 patients with two vessel disease, and 13 (28%) of the 47 patients with single vessel disease. Two (40%) of the five patients

without significant coronary artery disease had mild exertional angina at the one year follow up examination. Angina was therefore significantly more common in patients with multivessel (two or three vessel) disease, 24 (50%) (95% CI 35 to 65%) of 48 patients, than in patients with single vessel disease, 13 (28%) (95% CI 16 to 43%) of 47 patients ($p < 0.05$).

EJECTION FRACTION

At the time of cardiac catheterisation, the ejection fraction was $>50\%$ in 55 patients, 40–49% in 23 patients, 30–39% in 11 patients, and $<30\%$ in 10 patients. The quality of the left ventricular angiogram was not good enough for analysis in one patient.

ANGINA

Angina occurred in 31 patients during their six week exercise test (fig 1a). Of these, 25 (81%) (95% CI 62–92%) continued to experience angina during everyday life in the first year after infarction; but only 14 (20%) (95% CI 12 to 32%) of the 69 patients who had no angina on exercise testing ($p < 0.001$) did so. Of the 39 patients who experienced exertional angina during everyday life in the one year follow up period 36 (92%) had developed their first symptoms by the time they presented for their six week exercise test. Only 25 (69%) (95% CI 51 to 83%) of these 36 patients experienced angina during the exercise test, while two (5%) had significant ST segment depression alone and nine (25%) had a negative exercise test.

ST DEPRESSION

Significant ST depression occurred in 21 patients during their six week exercise test (fig 1b). Of these, five (24%) (95% CI 9–48%) experienced angina on exertion during follow up compared with 34 (43%) (95% CI 32–55%) of the 79 patients who did not have ST depression on exercise testing. This difference is not significant.

Only nine patients had ST depression of >2 mm

and of these, four (44%) (95% CI 15 to 77%) had a clinical history of angina during follow up compared with 35 (38%) (95% CI 28 to 49%) of the 91 patients with less or no ST depression. This difference is not significant.

DEATH

During the one year follow up period there was only one death in the study cohort (standardised mortality ratio $222 \pm 220\%$). Death was sudden and occurred 11 months after infarction. Necropsy did not show recent infarction, and death was assumed to be caused by an arrhythmia. This patient had single vessel right coronary artery disease and an ejection fraction of 36%; and six weeks after infarction he exercised for 18 minutes with a normal haemodynamic response, without angina, and with 1 mm ST segment depression in lead aVL only. There were six further deaths in the group of patients excluded from the study cohort and these are discussed below.

REINFARCTION

Reinfarction occurred in only three patients: one with single vessel circumflex disease and two with two vessel (left anterior descending and circumflex) disease. Of these three patients only one had angina during his exercise test and none had ST depression. The ejection fraction was 27% in one patient and $\geq 55\%$ in the other two.

CORONARY ARTERY SURGERY (fig 2)

Coronary artery surgery was performed on 15 patients during the one year follow up period with no operative mortality. Apart from two patients with significant narrowing of the left main stem, coronary artery surgery was performed only for limiting angina. Of these 15 patients, five had single vessel, seven had two vessel, and three had three vessel coronary artery disease. One of the patients with left main stem disease is included in the group with two vessel disease and the other in the group with three

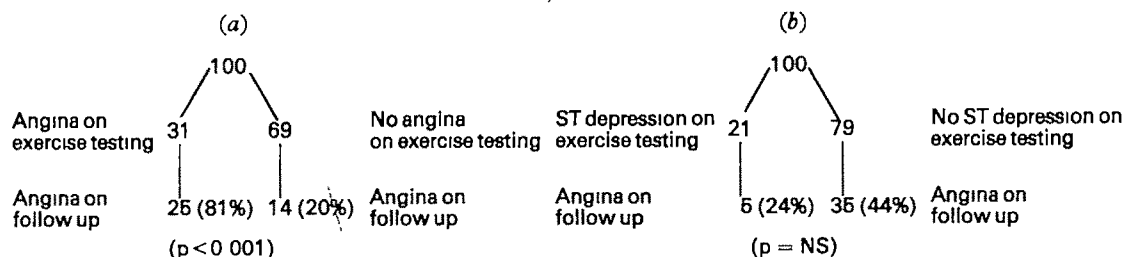


Fig 1 (a) Relation of occurrence of angina during follow up to angina on exercise testing and (b) to ST depression on exercise testing.

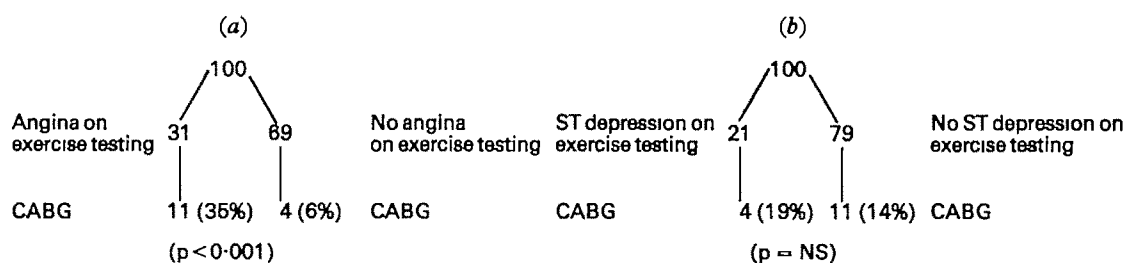


Fig 2 (a) Relation of coronary artery bypass grafting (CABG) during follow up to angina on exercise testing and (b) to ST depression on exercise testing.

vessel disease (there was additional significant right coronary artery disease).

Angina during the six week exercise test was an indicator of the later need for coronary artery surgery (fig 2a). Eleven (35%) (95% CI 19 to 54%) of the 31 patients with angina as the end point for their six week exercise test needed an operation and only four (6%) (CI 2 to 15%) of the 69 patients who did not develop angina ($p < 0.001$) later needed an operation.

Neither the presence of nor the degree of ST depression on exercise was a useful predictor of the need for subsequent coronary artery surgery (fig 2b). Four (19%) (95% CI 6 to 43%) of the 21 patients with ST depression and 11 (14%) (95% CI 8 to 24%) of the 79 patients without ST depression underwent coronary artery surgery during the first year of follow up ($p = \text{NS}$). Only one (11%) of the nine patients with ST depression of > 2 mm had coronary artery surgery.

Coronary artery surgery was needed in significantly more patients with impaired left ventricular function: eight (38%) (95% CI 19 to 61%) of the 21 patients with an ejection fraction $< 40\%$ but only seven (9%) (95% CI 4 to 18%) of the 78 patients with an ejection fraction $> 40\%$ ($p < 0.01$).

UNSTABLE ANGINA

There were no cases of unstable angina.

EXCLUDED PATIENTS

Six of the 70 patients who were not included in the study cohort died of cardiac causes in the first year of

follow up (standardised mortality ratio $1980 \pm 6530\%$). All deaths occurred suddenly at home in the first two months after discharge from hospital. Three died in the first three weeks—before the exercise test. Only one of these patients was excluded on medical grounds (because of severe systemic lupus erythematosus). The overall mortality for the 184 consecutive patients is, therefore, 3.8% (7/184).

Eight (11%) of these 70 patients had coronary artery surgery in the first year of follow up for limiting symptoms.

Three patients were lost to follow up.

Discussion

Prognostic information in subgroups of survivors of acute myocardial infarction can be applied to the management of these patients since those who have a good outlook can be reassured and those at increased risk of death and reinfarction can be investigated and managed appropriately.⁸⁻¹⁰ In recent years exercise testing soon after infarction has been suggested as one means of obtaining such information.¹⁻³ The increased workload on departments performing non-invasive tests is considerable when all patients are investigated. It is, therefore, important to identify patients in whom such an approach provides little additional information on which to base long term management. Most of the previous studies of exercise testing after myocardial infarction have included older patients,¹⁻³ and their conclusions may not be valid when applied to the management of younger patients in whom the outcome was better.⁴⁻⁶

Differences in study design, exercise test protocol and timing, and population selection make comparison between studies difficult. However, many workers have recommended an exercise test soon after infarction as a means of predicting significant cardiac events such as death and reinfarction, having shown that several variables identified during the exercise test correlate with a worse prognosis.^{11,12} Starling *et al* studied patients up to 79 years of age and found

Table Exercise test protocol (modified Bruce)

Stage	Speed (mph)	Gradient (%)
0	1.2	0
$\frac{1}{2}$	1.7	5
1	1.7	10
2	2.5	12
3	3.4	14
4	4.2	16
5	5.0	18

that a combination of angina, inadequate blood pressure response, and ST segment depression identified those patients with the highest mortality.² However, 24% of their patients had a history of previous myocardial infarction. In a similar study of patients up to 70 years of age, DeBusk *et al* found that exercise induced ST depression of at least 2 mm at a heart rate of <135 beats per minute predicted increased morbidity and mortality.¹³ The results of these and similar studies have been applied to the management of younger patients in whom the clinical course after infarction may be very different.

Studies of the course of disease in younger patients after infarction suggest that the outlook in patients under 60 years is very good.^{4,14,15} Roubin *et al* for instance, found a one year mortality of 3.6% in their study of 229 patients followed over a mean period of 34 months.¹⁴ No previous studies have reported on the correlation between exercise test data and prognosis in a young group of patients. Our study has therefore examined the outcome and the role of exercise testing six week after infarction in predicting important cardiac events in a consecutive series of patients under 55 years.

The study confirms that the prognosis in young survivors of myocardial infarction is very good. The inpatient mortality of 7.6% was similar to that reported by Norris *et al* in their study of 325 patients under 60 years of age.¹⁶ The overall mortality in the present series was only 3.8%; there was one death in those who underwent exercise testing and six among those who were excluded. The reasons for the increased mortality in those patients excluded from the study cohort is unclear. However, the calculated standardised mortality ratios of $222 \pm 220\%$ for the exercised patients and $1980 \pm 6530\%$ for the excluded patients show that the suggestion of a higher mortality rate amongst the "excluded" group is not an artefact of the age and sex distributions of the two populations. We confirmed that angina during the exercise test frequently predicted exertional angina during follow up. Interestingly, 92% of our patients with a history of exertional angina at one year follow up had experienced their first symptoms within six weeks of their acute infarction, although not all actually experienced it during the exercise test. As might be expected, the need for coronary artery surgery because of symptoms was significantly more common in patients with angina during the exercise test, a finding similar to that of Davidson and DeBusk.¹⁷ Neither ST segment depression nor an abnormal haemodynamic response to exercise was a useful predictor of subsequent cardiac events.

Naturally, our results must be examined against factors that might influence mortality, such as left ventricular function, coronary artery disease, coron-

ary artery surgery, and treatment with β blockers.

Taylor *et al* found that an ejection fraction of <40% and a history of previous myocardial infarction (probably operating through a reduced ejection fraction) were the best predictors of subsequent mortality over a 30 month follow up period.⁶ Norris *et al* also suggested that mortality was primarily related to left ventricular dysfunction, with exercise test variables and coronary artery disease playing a secondary role.¹⁶ Other evidence in favour of left ventricular dysfunction as a major prognostic factor has been provided by Sanz *et al*¹⁵ and De Feyter *et al*.¹⁸ An abnormal haemodynamic response to exercise (shown to relate to impaired left ventricular function) has been shown to correlate with outcome.^{2,11,19} In one study patients with an inadequate blood pressure response to exercise early after infarction had a mortality that was five times as high as that in patients in whom blood pressure rose by at least 30 mm Hg.¹¹ In that study 300 patients underwent exercise testing on a bicycle ergometer and the mortality rate in the 212 patients in whom the blood pressure increased by ≥ 30 mm Hg was 3% compared with 16% among the 88 patients in whom the blood pressure increased <30 mm Hg. An exercise induced reduction of >5% in left ventricular ejection fraction also identified patients at high risk of cardiac death and other cardiac events.²⁰ Conversely, a good haemodynamic response to exercise was used as a pointer to low risk patients.^{11,21} Seventy eight of our patients had ejection fractions >40% and 21 had ejection fractions <40%, figures that resemble those in other studies. In the present study, however, there was no correlation between exercise test variables such as short exercise time or an abnormal blood pressure response to exercise and either left ventricular function or subsequent prognosis.

The severity of coronary artery disease in our series is similar to that in previous studies. Twelve (12%) of our patients had three vessel disease compared with 7% and 9% respectively in the studies by De Feyter *et al*¹⁸ and Roubin *et al*¹⁴ in which the mortality rates in the first year of follow up were also low—between 3% and 4%.

Fifteen (15%) of our patients had coronary artery surgery during the year of follow up. This compares with 10–13.4% in the studies by Roubin *et al*,¹⁴ Krone *et al*,²² and De Feyter *et al*.¹⁸ Seventy seven (24%) of the 325 patients in the Norris study had coronary artery surgery in the first three months after infarction.¹⁶ In that study, however, the indications for operation were different from those used in this study. Some of their patients were operated on for limiting angina, others because of heart failure, and, in some, as part of a randomised study. In the present study, patients were only operated on for limiting

symptoms (with the exception of the two patients with stenoses of the left main stem) and, although our patients with low ejection fractions were more likely to have operation, in all cases they also had limiting angina. Most (70%) of our patients with low ejection fractions have not had an operation and only one of them has died.

β Blockers have been shown to produce a small but definite reduction in mortality after infarction^{23,24} but the rationale and cost benefit ratio of treating all patients after infarction need closer study. It was not our practice routinely to treat our patients with β blockers; we reserved them for specific indications such as angina or hypertension. The choice of antianginal preparation was left to the individual doctor, but at one year 22 patients were taking β blockers and less than half of them had been taking them for more than six months. Because mortality is worse in the first six months after myocardial infarction it is unlikely that β blockers had any significant effect on overall survival in this study.

The unique feature of our study population is their age. Davis *et al* in their study of 940 survivors of myocardial infarction under 66 years old, found that significantly more patients died in the 61–65 year age group than in the younger age groups.²⁵ Two further studies showed that apart from complex ventricular arrhythmias, age was the most important prognostic variable.^{26,27} The present study is thus further evidence that age is an important prognostic factor in survivors of myocardial infarction. Most of the patients with poor left ventricular function had angina and most of these could in turn be identified by a clinical history of angina as early as six weeks after infarction. Our findings suggest that routine angiography in all young patients after infarction is unnecessary although in the past, mainly for emotional reasons, this is the very patient group in which coronary arteriography has been used routinely. The exercise test six weeks after infarction provides little additional prognostic information for the first year follow up. It is chiefly performed to reassure both patient and clinician. Symptom free patients do not seem to need long term follow up but more prolonged study of the patients in this study may qualify this impression.

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Cardiac and whole body [^3H]noradrenaline kinetics in ischaemic heart disease: contrast between unstable anginal syndromes and pacing induced ischaemia

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SUMMARY Radiotracer kinetics were used to evaluate the activity of the sympathetic nervous system in 10 patients who had had unstable ischaemic symptoms within the previous 12 weeks and 10 with stable angina. Patients with recent unstable angina or angina after recent acute myocardial infarction had higher basal cardiac noradrenaline spillover than patients with stable angina. This represents a selective increase in cardiac sympathetic tone because whole body noradrenaline spillover was not significantly increased in the patients with recent unstable angina. Atrial pacing in 15 patients caused angina in 13 but did not significantly alter cardiac noradrenaline spillover in either patients with stable or unstable angina. The flow of plasma in the coronary sinus increased during pacing but because cardiac noradrenaline extraction decreased cardiac noradrenaline clearance was not significantly altered. Both whole body noradrenaline spillover and clearance were modestly increased by pacing, and arterial noradrenaline concentration was unchanged.

Patients with recent symptoms of unstable ischaemia had a sustained and selective increase in cardiac efferent sympathetic tone compared with patients with stable angina, and angina induced by atrial pacing did not cause important cardiac sympathetic activation.

The sympathetic nervous system has a profound effect on the susceptibility of the ischaemic myocardium to serious ventricular arrhythmias,^{1,2} and the cardiac autonomic nervous system has been implicated in sudden cardiac death.³ Experimental coronary occlusion, however, does not increase coronary venous overflow of noradrenaline^{4,5} but sympathetic responsiveness was temporarily related to vulnerability to arrhythmia in open chest anaesthetised dogs.⁶ Coronary occlusion increases local concentrations of cyclic adenosine monophosphate, possibly because of an increase in sympathetic activity.⁷ In addition to local exocytotic catecholamine release via reflex mechanisms or local nerve terminal depolarisation, ischaemia itself may result in the direct release of noradrenaline via outward transport from the nerve terminal mediated by a carrier.⁸ Little is known about the response of the sympathetic nervous system to myocardial ischaemia in human beings.

Assessment of sympathetic tone in clinical research has often been based on the measurement of concentrations of noradrenaline in the venous plasma for overall sympathetic tone and of the venoarterial difference in noradrenaline concentration for sympathetic tone to individual organs. These methods, however, disregard the influence of noradrenaline clearance. Recently developed radiotracer kinetic techniques, with infusions of [^3H]noradrenaline, can simultaneously assess noradrenaline spillover to plasma and noradrenaline clearance.⁹ These radiotracer techniques assume that a steady state has been reached, that infused [^3H]noradrenaline is not re-released to an appreciable degree, and that alumina extractable [^3H]metabolites do not accumulate during infusion. Our own studies¹⁰ and those of Esler *et al*¹¹ have shown these assumptions to be valid. Although this technique measures noradrenaline spillover to plasma and not noradrenaline release, it has been shown for several organs, including the heart,¹² that regional noradrenaline spillover correlates well with the rate of direct sympathetic nerve stimulation.¹³ Thus these techniques allow a better assessment of cardiac sympathetic activity than was possible before.

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The aim of this study was to evaluate the effects on cardiac and overall sympathetic activity in patients with coronary artery disease of recent unstable ischaemic symptoms and of a short period of myocardial ischaemia induced by atrial pacing.

Patients and methods

PATIENTS

We studied 20 patients (table 1) while they were supine and in the fasting state one hour after diagnostic cardiac catheterisation. Nineteen were male and all had coronary arterial disease (>50% stenosis of the diameter of at least one major coronary artery). All patients were stabilised on medical treatment at the time of study. Ten patients had unstable ischaemic symptoms (sudden deterioration of previously stable angina, onset of angina at rest, or angina after acute myocardial infarction) within the previous 12 weeks (group 1) and 10 had angina which had been stable for at least 12 weeks (group 2). Four of group 2 and three of group 1 had systemic hypertension and none was on a sodium restricted diet. The resting left ventricular ejection fraction was

determined from the right anterior oblique cine-angiogram.¹⁴ The two groups were well matched for age, extent and severity of coronary disease, and for medical treatment. Blood pressure and left ventricular end diastolic pressure were higher in group 2 but the left ventricular ejection fraction was not significantly different. All subjects gave informed consent to the study, which was approved by the Central Oxford Research Ethics Committee.

PROTOCOL

After left ventricular and coronary angiography, performed by the standard femoral approach, a sampling catheter was left in the artery and a Bain flow catheter (Electro-catheter Corporation, New Jersey) was inserted under fluoroscopic control via the right subclavian vein into the distal coronary sinus. Correct placement was confirmed by injection of a small quantity of contrast material. This catheter permitted repeated sampling of blood from the coronary sinus and measurement of blood flow in the coronary sinus by thermodilution.¹⁵ For measurement of blood flow in the coronary sinus we infused 0.9% saline at room temperature via a

Table 1 Clinical data and results of cardiac catheterisation for 20 patients with ischaemic heart disease

Case No	Age (yr)	BP (mm Hg)	LVEF (%)	LVEDP (mm Hg)	CAD	Drugs	ETT
Group 1 (n = 10) (recent unstable ischaemic symptoms).							
1	58	110/68	70	11	LAD,Cx,RCA	Met,nif,ISDN	St 2, 3 mm, ant-lat
2	58	155/82	64	10	LAD,Cx	Frus,amil,ISDN	—
3	61	120/72	52	12	LAD,Cx,RCA	Met,ISDN,asp	St 2, 2 mm, inf-lat
4	58	125/85	36	18	Cx,RCA	Met,frus,amil,ISDN	St 3, ST↑, inf
5	56	110/70	54	10	LAD,RCA	At,asp,thiaz	—
6	51	174/92	71	14	RCA	At,thiaz	St 2, 2 mm, inf-lat
7	68	155/94	74	11	LAD,Cx,RCA	At,dilt,GTN	St 2, 3 mm, lat
8	48	105/70	55	16	Cx,RCA	At,asp	St 3, 2 mm, lat
9	57	160/85	60	10	LAD,Cx,RCA	At,nif,asp	St 1, 5 mm, lat
10	58	148/88	62	10	LAD,Cx	At,ISDN,asp	St 2, no ST↓
Mean (SEM)	57 (2)	136/81 (8/3)	60 (4)	12 (0.9)			
Group 2 (n = 10) (stable angina):							
11	57	100/62	46	10	LAD,Cx,RCA	Aceb,ISDN	St 3, 6 mm, inf-lat
12	57	122/70	64	10	LM,Cx,RCA	Prop,asp	St 3, 3 mm, ant-lat
13	60	115/55	52	8	LAD,Cx,RCA	At,nif,ISDN	St 2, 3 mm, inf-lat
14	72	135/58	70	8	LAD,Cx,RCA	At,nif,ISDN	St 1, 3 mm, inf-lat
15	53	112/65	61	12	LAD,Cx,RCA	At,nif,ISDN,asp	St 3, 2 mm, lat
16	53	115/82	64	8	LAD,Cx,RCA	Dilt,ISDN,asp	St 2, 2 mm, inf-lat
17	54	100/55	67	10	LAD	At,nif	St 2, 2 mm, lat
18	61	92/50	71	8	LM,LAD,Cx,RCA	Prop,asp	St 1, 2 mm, inf-lat
19	55	135/85	75	9	LAD,RCA	At,nif,thiaz	St 3, no ST↓
20	58	105/70	70	8	LAD,Cx,RCA	At,nif,ISDN	St 3, 1 mm, inf-lat
Mean (SEM)	58 (2)	113*/65** (5/4)	65 (3)	9* (0.4)			

*p < 0.05, **p < 0.01 group 1 versus group 2 (non-paired t test).

Aceb, acebutolol; amil, amiloride; ant-lat, anterolateral (V2-V6); asp, aspirin; at, atenolol; BP, blood pressure; CAD, extent of coronary artery disease; cap, captopril; Cx, circumflex coronary artery; dilt, diltiazem; ETT, result of exercise tolerance test (stage reached, amount and localisation of ST segment depression); frus, frusemide; GTN, glyceryl trinitrate; inf, inferior (2,3, aVF); inf-lat, inferolateral (2,3,aVF,V5,V6); ISDN, isosorbide dinitrate; LAD, left anterior descending artery; lat, lateral (V5,V6 ± 1, aVL); LM, left main coronary artery; LVEF, left ventricular ejection fraction; LVEDP, left ventricular end diastolic pressure; met, metoprolol; nif, nifedipine; prop, propranolol; RCA, right coronary artery; St, stage (standard Bruce protocol) reached on exercise testing; ST↓, ST segment depression; ST↑, ST segment elevation; thiaz, thiazide diuretic.

Harvard pump at 28 ml/min until equilibrium was reached (15–30 seconds). Measurements were made in quiet held respiration to minimise respiratory movement of the catheter. The output from the Baim Coronary Sinus Flow Analyser (Electro-catheter Corporation) was linked to a Hewlett-Packard 9000 217 computer to give on line measurement of blood flow in the coronary sinus by use of the standard equation to determine flow from the temperature drop, integrated over a five second period. The system gave reproducible measurements of coronary sinus flow, which were made in duplicate. The coefficient of variation between repeated single measurements at rest was 3%. Plasma flow in the coronary sinus was calculated by correction for the arterial haematocrit. Cardiac catheterisation was uncomplicated in all patients and none developed symptomatic myocardial ischaemia during the procedure.

After insertion of the Baim catheter subjects were transferred to the research laboratory, where the [^3H]noradrenaline infusion was started. Samples of arterial blood and blood from the coronary sinus were taken 30 minutes after the start of the infusion. In 10 subjects with stable angina and five subjects with unstable symptoms atrial pacing via the Baim catheter was then started and the rate was increased to the maximum sustainable rate (the fastest rate not causing severe angina or Wenckebach atrioventricular block). Pacing increased the heart rate from 62 beats/minute at rest (range 48–70) to 110 (94–123) beats/minute. In 13 patients angina developed during pacing. In nine of these ST segment depression on the standard 12 lead surface electrocardiogram was ≥ 1 mm. Arterial and coronary sinus blood samples (10 ml each) were taken after 10 and 20 minutes pacing and again 10 minutes after the end of pacing. Coronary sinus blood flow was measured immediately before each sampling time.

NORADRENALINE KINETICS

Noradrenaline kinetics were measured according to the techniques of Esler *et al.*¹¹ 1-[2,5,6- ^3H]noradrenaline (New England Nuclear) was given intravenously as a bolus (12 μCi (0.44 MBq) followed by constant infusion (0.7 μCi (0.026 MBq) $\text{min}^{-1}\text{m}^{-2}$) for up to 80 minutes. Blood samples were collected into chilled lithium heparin tubes, centrifuged at 4°C, and the plasma was frozen on dry ice and stored at -20°C for up to three months. Sodium metabisulphite at a final concentration of 1 mmol/l was used as an antioxidant. Plasma noradrenaline was measured by high performance liquid chromatography.¹⁶ The normal range in our laboratory is 120–300 pg/ml and the within day coefficient of variation is 4%. Plasma [^3H]noradrenaline was measured by liquid scintillation counting of

alumina extracts with correction for recovery of a non-radioactive internal standard (dihydroxybenzylamine).¹⁰ The within day coefficient of variation for the estimation of [^3H]noradrenaline is 7%. Each sample was assayed in duplicate, with half of each alumina extract being used for estimation of [^3H]noradrenaline and half for estimation of noradrenaline and dihydroxybenzylamine.

Noradrenaline (NA) plasma clearance and noradrenaline spillover to plasma for the heart and whole body were measured according to the following relations, which hold under steady state conditions¹¹:

$$\text{Whole body NA clearance} = \frac{\text{Infusion rate (dpm/min)}}{\text{Plasma } [^3\text{H}] \text{ NA (dpm/ml)}}$$

$$\text{Whole body NA spillover} = \frac{\text{Infusion rate (dpm/min)}}{\text{Specific radioactivity of plasma NA (dpm/pg)}}$$

$$\text{Cardiac NA clearance} = \text{CSPF} \times \text{NA}_E$$

$$\text{Cardiac NA spillover} = \text{CSPF} \times [(\text{NA}_{\text{CS}} - \text{NA}_A) + (\text{NA}_A \times \text{NA}_E)]$$

where CSPF = coronary sinus plasma flow; NA_E = fractional extraction of [^3H]noradrenaline by the coronary circulation; NA_{CS} = coronary sinus noradrenaline concentration; NA_A = arterial noradrenaline concentration; and dpm = disintegrations per minute of [^3H]noradrenaline.

STATISTICAL ANALYSIS

Analysis of variance was used to assess the differences between the data at the four time points of the pacing protocol. The data on noradrenaline kinetics were log transformed because their distribution was skewed. Differences between patients with stable and unstable symptoms were analysed by a two tailed Mann-Whitney U test. Results were deemed to be significant at the 5% level. Results are expressed as the mean (1 SEM).

Results

BASAL NORADRENALINE KINETICS IN PATIENTS WITH STABLE AND RECENT UNSTABLE SYMPTOMS (table 2, figs 1 and 2)

The ranges of basal concentrations of noradrenaline in the coronary sinus (62–1438 pg/ml) and of basal cardiac noradrenaline spillover (2–76 ng/min) were large. Patients with chronic stable angina had much lower concentrations of noradrenaline in the coronary sinus and much lower cardiac noradrenaline spillover than did patients with recent unstable ischaemic symptoms. Values were highest in a man

Table 2 Basal noradrenaline kinetics in patients with recent unstable or stable symptoms

Case No and history	Cardiac NA spillover (ng/min)	Cardiac NA clearance (ml/min)	CS NA (pg/ml)	Art NA (pg/ml)	Total NA spillover (ng/min)	Total NA clearance (ml/min)
Group 1 (n = 10) (recent unstable ischaemic symptoms).						
(1) 8/52 unstable AP	10	49	210	214	197	919
(2) 2/52 unstable AP → pulmonary oedema	76	35	1438	814	649	797
(3) 6/52 unstable AP	14	47	470	274	335	1222
(4) AMI 6/52 previously → ventricular aneurysm	49	24	839	271	335	783
(5) HT, non Q-wave AMI 8/7 previously → continued AP	26	52	449	271	483	1784
(6) HT, 12/52 unstable AP	20	41	387	207	386	1866
(7) 2/12 unstable AP	6	29	222	267	374	1401
(8) Non Q-wave AMI 2/52 previously → continued AP	12	23	380	158	236	1494
(9) HT, 2/12 unstable AP	17	44	296	132	168	1296
(10) Non Q-wave AMI 10/52 previously → continued AP	15	33	456	408	686	1680
(1-10) Mean (SEM)	24 (7)	38 (3)	515 (117)	317 (63)	385 (56)	1325 (125)
Group 2 (n = 10) (stable angina):						
(11) Previous AMI, 10 yr class II AP	9	31	331	452	380	820
(12) HT, previous AMI, MR, 1 yr class II AP	4	27	179	208	182	875
(13) 1 yr class III AP	2	32	62	114	315	2766
(14) HT, 6/12 class IV AP	14	64	202	178	246	1406
(15) Previous AMI and CABG, 1 yr class III AP	2	25	94	179	248	1387
(16) Previous AMI, 5/12 class III AP, unstable AP 5/12 ago	12	49	226	200	93	467
(17) 18/12 class II AP	2	47	84	98	156	1598
(18) HT, previous CABG, 4/12 class III AP	8	45	180	218	317	1455
(19) HT, 18/12 class III AP	5	33	163	197	346	1757
(20) 4/12 class II AP	4	23	194	248	310	1249
(11-20) Mean (SEM)	6 (1)*	38 (4)	171 (24)*	210 (30)	257 (25)	1416 (182)

* $p < 0.001$, group 1 v group 2, Mann-Whitney U test.

AMI, acute myocardial infarction; AP, angina pectoris, Art, arterial; CABG, coronary artery bypass grafts; class, New York Heart Association class; CS, coronary sinus; HT, systemic hypertension; MR, mitral regurgitation; NA, noradrenaline.

Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

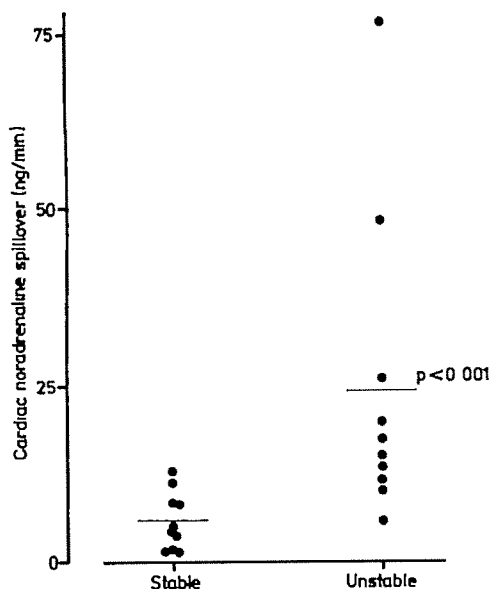


Fig 1 Cardiac noradrenaline spillover in patients with stable and unstable symptoms. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

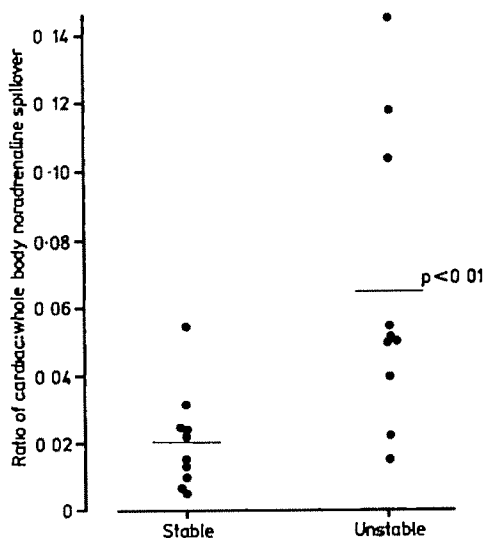


Fig 2 Cardiac to whole body noradrenaline spillover ratio in patients with stable and unstable symptoms.

with a two week history of unstable angina, culminating in severe pulmonary oedema (patient 2, table 2). Myocardial infarction was excluded and when cardiac catheterisation was performed a week later, after the resolution of the pulmonary oedema, severe three vessel coronary artery disease was found. There was some anteroapical hypokinesis but left ventricular contraction was good overall (left ventricular ejection fraction = 64%). Mean cardiac noradrenaline spillover in the 10 patients with recent unstable ischaemic symptoms was 24 (7) ng/min compared with 6 (1) ng/min for the 10 patients with stable angina ($p < 0.001$, fig 1). Coronary sinus noradrenaline concentration was also significantly greater in the patients with recent unstable angina ($p < 0.001$, table 2).

In contrast with coronary venous noradrenaline concentration and spillover, arterial noradrenaline concentration was not significantly higher in the group with recent unstable angina (317 (63) pg/ml versus 210 (30) pg/ml). Similarly, whole body noradrenaline spillover was not significantly higher in this group (385 (56) ng/min versus 257 (25) ng/min). Whole body noradrenaline clearance was similar in both groups (table 2).

The ratio of cardiac noradrenaline spillover in the group with recent unstable angina compared with that in the patients with stable angina was 4.0:1. For whole body spillover the ratio between the same two groups was only 1.5:1. Similarly the ratio of cardiac to whole body noradrenaline spillover was greater in the group with recent unstable angina (0.065 (0.013)) than in the group with stable angina (0.021 (0.005)) ($p < 0.01$, fig 2), so there was evidence of a selective increase in cardiac sympathetic activity in patients with recent unstable angina.

There was no significant correlation between left ventricular ejection fraction and cardiac noradrenaline spillover ($r = -0.30$, $p = \text{NS}$). Similarly there was no significant correlation between left ventricular end diastolic pressure and cardiac noradrenaline spillover ($r = 0.36$, $p = \text{NS}$).

NORADRENALINE KINETICS DURING ATRIAL PACING (figs 3, 4, 5, and 6)

Atrial pacing increased coronary sinus plasma flow from 55 (5) ml/min to 78 (7) ml/min but, as a result of a decline in the fractional extraction of noradrenaline by the coronary circulation from 71 (3)% to 59 (4)%, cardiac noradrenaline clearance was not significantly altered by pacing (fig 3). Despite the development of myocardial ischaemia in most of the subjects there was a trend towards a decline in coronary sinus noradrenaline concentration during atrial pacing and cardiac noradrenaline spillover was unchanged (fig 4). No consistent trend in cardiac noradrenaline

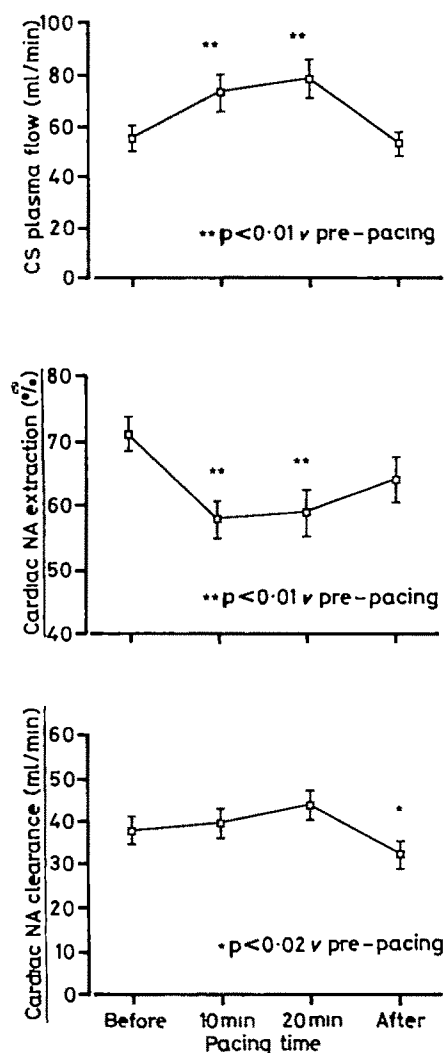


Fig 3 Coronary sinus (CS) plasma flow, cardiac noradrenaline (NA) extraction, and cardiac noradrenaline clearance in response to atrial pacing.

spillover was seen in response to atrial pacing in either groups (stable $n = 10$, unstable $n = 5$) (fig 5).

Atrial pacing resulted in a modest rise in whole body noradrenaline clearance, from 1311 (138) ml/min to 1508 (213) ml/min. This was associated with a small rise in noradrenaline spillover to plasma and no change in arterial noradrenaline concentration (fig 6). There was no difference in the cardiac or whole body noradrenaline kinetics between 10 and 20 minutes pacing, confirming that a new steady state had been reached.

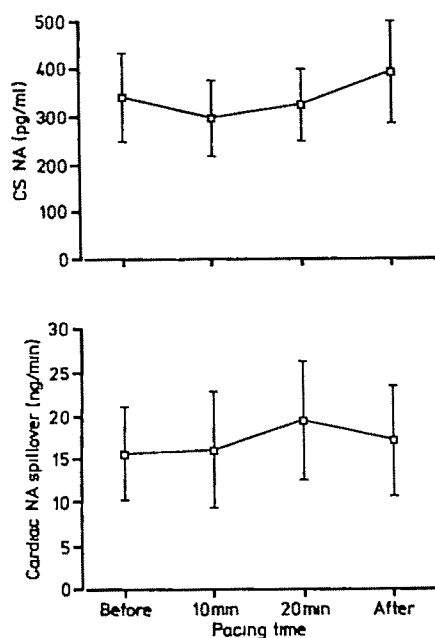


Fig 4 Coronary sinus (CS) noradrenaline (NA) concentration and cardiac noradrenaline spillover in response to atrial pacing to ischaemia. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

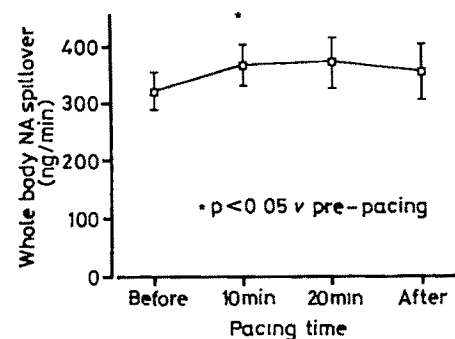
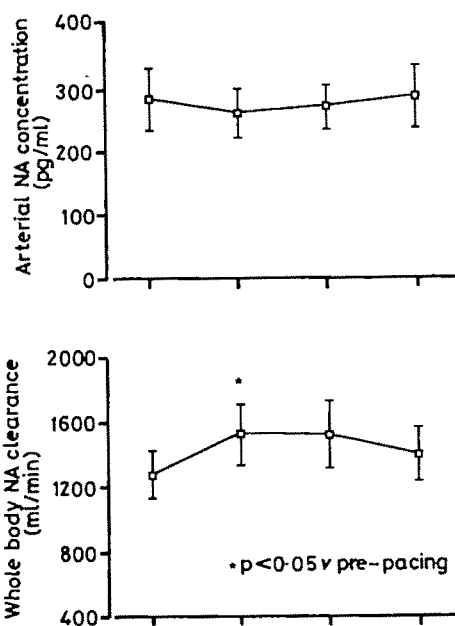


Fig 6 Whole body noradrenaline (NA) kinetics in response to atrial pacing. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

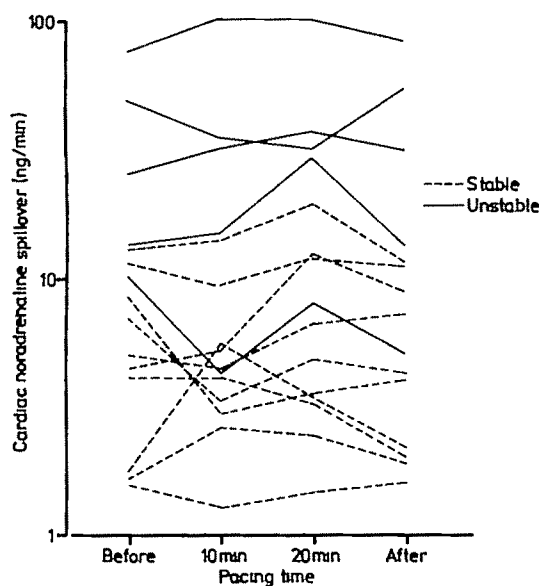


Fig 5 Cardiac noradrenaline spillover during atrial pacing in 15 patients—10 with stable angina and five with recent unstable ischaemic symptoms. Conversion factor: noradrenaline—1 ng/ml = 5.91 nmol/l.

Discussion

SYMPATHETIC ACTIVITY IN ISCHAEMIC HEART DISEASE

It is widely believed that angina and myocardial ischaemia give rise to a generalised increase in sympathetic tone.¹⁷ Few studies have, however, investigated this belief or attempted to define cardiac sympathetic tone during myocardial ischaemia. Those studies which have measured catecholamine concentrations in ischaemic heart disease have not taken into account the influence of noradrenaline clearance. All organs both extract noradrenaline from and secrete noradrenaline into the circulation,

and at rest the heart, with its rich sympathetic innervation, extracts about 70% of the noradrenaline entering the coronary circulation. Because, as this study shows, cardiac noradrenaline uptake may be profoundly altered by manoeuvres that alter blood flow, it is not possible to come to meaningful conclusions about the sympathetic tone to a given organ simply by measuring venoarterial differences in noradrenaline concentration and organ blood flow. The use of steady state radiotracer methods overcomes this difficulty and allows sympathetic tone to be more reliably estimated.

Two previous studies have evaluated concentrations of catecholamine in the coronary sinus during atrial pacing to ischaemia in man. One found that "myocardial noradrenaline release" increased in response to atrial pacing but to a greater extent in normal controls than in patients with ischaemic heart disease.¹⁸ A modest increase in concentration of noradrenaline in the coronary sinus was shown during atrial pacing to angina but there was no significant increase in arterial noradrenaline concentration. The second, conversely, reported a decrease in "myocardial noradrenaline overflow" during atrial pacing to angina, and showed a modest increase in arterial noradrenaline concentration but no significant change in coronary sinus noradrenaline.¹⁹ In anaesthetised dogs epicardial pacing did not increase cardiac noradrenaline spillover.¹² Robertson *et al* measured coronary sinus and arterial noradrenaline concentrations during the course of spontaneous coronary artery spasm.²⁰ No changes were seen early during ischaemia. Towards the end of ischaemia both arterial and coronary sinus concentrations of noradrenaline were increased, although venoarterial difference in concentration was little changed and coronary sinus blood flow was not measured.

Hasking *et al* measured resting cardiac noradrenaline spillover using radiotracer techniques in 15 subjects with normal left ventricular function, of whom five had ischaemic heart disease, and found mean cardiac noradrenaline spillover to be 5 ng/min¹³; this accorded with the findings in the present study, but no previous study has used radiotracers to assess the response of the sympathetic nervous system to myocardial ischaemia in man.

BASAL NORADRENALINE KINETICS IN ISCHAEMIC HEART DISEASE

In subjects with stable angina cardiac and whole body noradrenaline spillover were similar to those previously reported for normal subjects²¹ and to our patients with normal coronary arteries undergoing coronary arteriography (unpublished data). There is, therefore, no evidence of either generalised or cardiac sympathetic overactivity in stable angina, even when

the angina is severe and the underlying coronary disease extensive. Those with similar severity of underlying disease but with unstable ischaemic symptoms within the previous 12 weeks had much higher basal cardiac noradrenaline spillover than patients with stable angina, although whole body noradrenaline spillover was not significantly different. This represents a selective and sustained increase in cardiac efferent sympathetic tone in these high risk patients.

Although systemic hypertension was diagnosed in similar numbers of patients in each group, blood pressure was significantly higher in the group with recent unstable angina. Transient hypertension has been used as a marker of sympathetic overactivity²² and it is not unexpected that blood pressure was higher in the group of patients in whom considerable cardiac sympathetic activation was shown.

Unstable angina, acute myocardial infarction, and sudden ischaemic cardiac death are all believed to be initiated by a rapid increase in luminal narrowing of a coronary artery by an unstable atherosclerotic plaque. This change in luminal narrowing is believed to be caused by the pathological process of plaque rupture and haemorrhage and thus unstable angina, myocardial infarction, and sudden cardiac death are probably a range of clinical manifestations of one pathological process.²³ Which clinical path an individual patient will follow depends partly upon the severity, duration, and extent of the resulting myocardial ischaemia, but the occurrence of sudden death depends also on the susceptibility of the ischaemic myocardium to serious ventricular arrhythmias, and here the sympathetic nervous system may have a pivotal role. Although sudden cardiac death is usually associated at necropsy with an acute coronary arterial lesion,²⁴ survivors resuscitated from out of hospital ventricular fibrillation ("failed sudden death") do not usually sustain a myocardial infarction.²⁵

This study has shown increased cardiac sympathetic activity in patients with recent unstable ischaemic symptoms. This suggests that acute coronary arterial lesions, causing unstable angina or acute myocardial infarction and carrying an increased risk of sudden death,²⁶ are associated with pronounced cardiac sympathetic activation.

NORADRENALINE KINETICS DURING ATRIAL PACING

We found no consistent changes in arterial or coronary sinus noradrenaline concentration in response to atrial pacing and indeed the trend was for coronary sinus noradrenaline to decrease. Cardiac noradrenaline spillover to plasma was not increased by atrial pacing in either stable or unstable angina (fig 6)

despite the development of angina in most patients. There is thus no evidence that myocardial ischaemia per se, at least of the degree induced in this study, causes cardiac or generalised sympathetic activation.

LIMITATIONS OF THE STUDY

Regional heterogeneity within the heart

Sampling from the coronary sinus does have certain theoretical disadvantages. Samples taken from this site during angina will inevitably contain venous effluent from both ischaemic and non-ischaemic areas and the relative contribution of each is not assessable. In the dog model it is possible to cannulate local veins from ischaemic and non-ischaemic territories⁶ but this cannot be done in man. However, the severity and distribution of the coronary disease in our subjects make it highly likely that, when they developed myocardial ischaemia, the coronary sinus samples contained a substantial proportion of venous effluent from ischaemic myocardium (14 of the 15 paced patients had significant disease of the left anterior descending artery and 12 had significant disease of the circumflex artery). Thus any important increase in cardiac sympathetic activity, whether or not it was localised to the ischaemic area, should have been detectable.

Medications

All the patients in the study were on antianginal medication, which we and our ethics committee felt should not be withdrawn. The possibility that this may have modified the sympathetic response to myocardial ischaemia cannot be excluded. Although β adrenoreceptor antagonists (the most likely drugs to alter sympathetic activity) decrease noradrenaline clearance, at least in the short term, they do not change total noradrenaline spillover.⁴⁷ It therefore seems unlikely that the patients' drug treatment was responsible for the observed lack of increase in cardiac noradrenaline spillover when myocardial ischaemia was induced by atrial pacing.

Variation between patient groups

All patients had been stabilised on medical treatment before study and at the time of study showed no evidence of myocardial ischaemia. Left ventricular function was slightly worse in the patients with recent unstable ischaemic symptoms than the patients with stable angina, as shown by higher left ventricular end diastolic pressure and slightly but not significantly lower resting left ventricular ejection fraction. However, overall left ventricular function was good in both groups and there was no significant correlation between left ventricular ejection fraction or left ventricular end diastolic pressure and cardiac noradrenaline spillover. Thus the substantial cardiac sympathetic overactivity shown in the unstable

group was not the result of impaired left ventricular function.

Four of the patients in the unstable group were receiving diuretic drugs (patients 2, 4, 5, and 6, table 1)—two for pulmonary congestion and two for hypertension. All four had high cardiac noradrenaline spillover. Only one patient in the stable group (patient 19) was receiving diuretics and he did not have high cardiac noradrenaline spillover. Diuretics were associated with a 40% increase in whole body noradrenaline spillover in the only study in which this has been assessed,⁹ so diuretics may have contributed to the cardiac sympathetic activation seen in some of our patients. However, the magnitude of the increases in cardiac noradrenaline spillover makes it unlikely that they were caused solely by diuretics and even if the two patients on loop diuretics for pulmonary congestion are excluded from the analysis the difference between the stable and the unstable groups remains significant at the 1% level. The observed differences between the groups are, therefore, not the result of a diuretic effect. In other respects the stable and unstable groups were well matched (table 1).

CLINICAL RELEVANCE OF THE STUDY

Many experimental studies have shown that the combination of myocardial ischaemia and sympathetic stimulation is a powerful cause of ventricular arrhythmias, which are responsible for sudden cardiac death in most cases.³⁷ It is likely that the arrhythmogenic action of sympathetic stimulation operates at several levels and sensitises the myocardium to the arrhythmogenic effects of myocardial ischaemia through various mechanisms, including coronary blood flow regulation, myocardial oxygen demand, and promotion of automatic and re-entrant pathways and triggered activity.²⁸

The demonstration in this study of increased cardiac sympathetic tone in unstable ischaemic syndromes is therefore of considerable importance in view of the increased risk of sudden death in such patients. The benefit in terms of mortality that is associated with the use of β blockers after myocardial infarction is due to a reduction in sudden death,²⁹ and a reduction in the response of the target organ to sympathetic stimulation may be the mechanism for this protective effect.

The cause of the cardiac sympathetic activation in unstable ischaemic syndromes is not clear. An excitatory cardio-cardiac sympathetic reflex elicited by myocardial ischaemia exists³⁰ and such reflexes may have a role, albeit that at the time of these studies there was no evidence of continuing myocardial ischaemia at rest. Some aspect of the unstable ischaemic syndromes seems to give rise to a sustained activation of the cardiac sympathetic nerves but

whether this relates to the length and severity of myocardial ischaemia or to some more basic response to the process of plaque rupture and haemorrhage or to the presence of intracoronary platelet emboli²⁴ cannot, at present, be ascertained. Differential organ-specific activation of the sympathetic nerves to the heart and kidneys has been shown in patients with cardiac failure¹⁵ and such patients are also known to be at high risk of sudden death secondary to ventricular arrhythmias.³¹ Sustained cardiac sympathetic overactivity persisting six months after acute myocardial infarction has also recently been shown by power spectrum analysis of heart rate variability.³²

This study shows that patients with recent unstable ischaemic symptoms suggestive of an acute coronary arterial lesion have evidence of a sustained increase in cardiac efferent sympathetic tone, whereas moderate myocardial ischaemia induced by atrial pacing does not cause important cardiac sympathetic activation. These data may in part explain the worse prognosis and increased risk of sudden death in unstable angina and support the theory that sympathetic overactivity and myocardial ischaemia are important interacting factors in the pathogenesis of serious ventricular arrhythmias and sudden cardiac death in ischaemic heart disease.

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Left ventricular filling and early diastolic function at rest and during angina in patients with coronary artery disease

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SUMMARY Left ventricular diastolic function was studied in 11 patients with coronary artery disease. Single plane ventriculography (30° right anterior oblique projection) was performed at rest and during an episode of angina immediately after a period of rapid atrial pacing. Left ventricular pressure was recorded simultaneously by a micromanometer tipped catheter. The ventriculograms were digitised frame by frame to derive continuous plots of left ventricular shape, volume, and rate of change of volume. The time constant (τ) of the fall in left ventricular pressure was determined from the exponential portion of pressure decay during isovolumic relaxation. Ventricular pressure-volume loops were constructed to study the left ventricular diastolic pressure-volume relation. The time of minimum left ventricular pressure was used to divide diastole into an early phase and a late phase. Angina was associated with an increase in end systolic volume and a fall in ejection fraction with no significant change in end diastolic volume. Peak left ventricular pressure was unchanged but left ventricular minimum and end diastolic pressures were both increased and the diastolic pressure-volume relation was moved upwards. The time constant of left ventricular pressure fall was prolonged. At rest more than 50% of the stroke volume entered the left ventricle during the period of early diastole. This proportion was significantly reduced during angina and as a consequence a significantly greater proportion of the stroke volume entered the ventricle during late diastole. Despite this, and although the left ventricular diastolic pressure-volume relation was moved upwards with angina, the mean slope of the relation during late diastole—that is, chamber stiffness—was not significantly altered. The upward shift of the left ventricular diastolic pressure-volume relation seen during angina is thus already apparent in early diastole, and its extent does not change during the later phase of diastole, which alone shows the property of passive stiffness. A primary increase in the passive stiffness of the ventricle cannot therefore be the cause of the upward shift of the diastolic pressure-volume relation, and events occurring in early diastole have to be looked to for an explanation.

The study findings show that left ventricular function in early diastole is profoundly disturbed during angina pectoris and it is suggested that loss of elastic recoil and dissipation of this restoring force by asynchronous onset of relaxation and abnormal changes in shape are important factors contributing to this disturbance of function.

An increase in left ventricular end diastolic pressure and an upward shift of the left ventricular diastolic pressure-volume relation are well recognised haemodynamic consequences of myocardial ischaemia.^{1,2} Various explanatory mechanisms have

been postulated, including loss of elastic recoil^{3,4} and dissipation of this restoring force by asynchronous wall motion during ventricular relaxation,^{5,6} external restraint of the left ventricle by the right ventricle and a constraining pericardium,⁷ and, most frequently cited, increases in chamber stiffness due either to delayed deactivation of actin-myosin cross bridges in ischaemic regions of the myocardium^{8,9} or to increased myocardial turgor.¹⁰ Ventricular relaxation

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and filling, however, are such complex processes that they are unlikely to be determined by any single factor and it is probable that each of these mechanisms affects function at some time during the diastolic period. In the present study therefore we used the point of minimum left ventricular pressure to divide diastole into an early and a late phase to try to understand how in patients with coronary artery disease an episode of angina induced by rapid atrial pacing modifies left ventricular function in early diastole, and the effect these abnormalities have on later diastolic events.

Patients and methods

PATIENTS AND CATHETERISATION PROCEDURE

Studies were performed at the time of diagnostic catheterisation in 11 male patients (mean age 52 years, range 42–68 years). All patients had chronic stable exertional angina and all had appreciable (>70%) obstructive coronary artery disease (four single, one double, and six triple vessel disease). Four of the patients had had a previous myocardial infarction. All medications, except glyceryl trinitrate, were stopped at least 15 hours before catheterisation, which was performed without premedication.

The study protocol was approved by the ethics committee of the Brompton Hospital and involved the performance of two left ventricular cineangiograms—the first at rest and the second during an episode of angina induced by rapid atrial pacing. The two cineangiograms were performed at least 20 minutes apart and on each occasion we used identical cine frame speeds (50/second), radiographic projections (30° right anterior oblique), quantities of contrast agent (50 ml of Urografin 370, meglumine diatrizoate), and flow rates (12 ml/s). Unfiltered high fidelity left ventricular pressure was measured during each contrast injection by a Gaeltec catheter tip pressure transducer and was recorded, together with an electrocardiogram, on a strip chart at a paper speed of 200 mm/s. The micromanometer signal was calibrated by superimposing it on a left ventricular pressure pulse derived from a conventional fluid filled manometer system.

To provoke an episode of angina patients were paced from the right atrial appendage with a Zucker pacing catheter. Pacing was initiated at 100 beats/min and the rate was increased by 10 beats/min every two minutes up to a maximum of 150 beats/min. When the patient indicated that he was experiencing angina of an intensity at which he would normally need to rest or to take a glyceryl trinitrate tablet, pacing was abruptly stopped and the second left ventricular cineangiogram was performed almost immediately (5–10 seconds later) with the patient in sinus rhythm.

ANALYSIS OF DATA

The left ventricular cineangiograms were digitised frame by frame.¹¹ A calibration value was obtained by displacing the catheter table 10 cm. Frames were related to each other by means of a fixed external reference point.¹² Beats used for analysis had occurred within five cycles from the start of contrast injection (when the effects of contrast on left ventricular function are negligible¹³), showed complete cavity opacification, and were not postextrasystolic. A mark on the cinefilm produced by an electrocardiographically gated light emitting diode in the cinecamera shutter plane assembly enabled the end diastolic frame to be identified. Plots were generated (fig 1) to show the following variables continuously

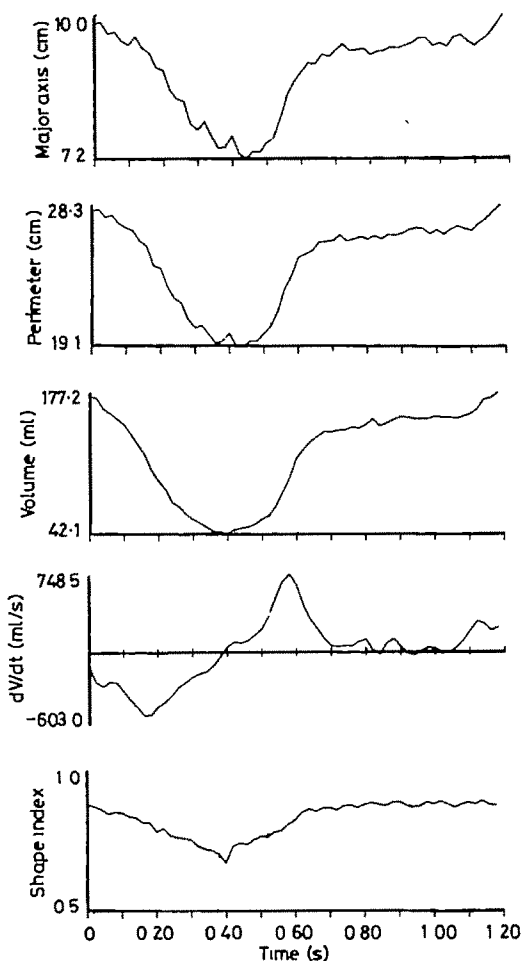


Fig 1 Computer generated plot showing changes in length of the ventricular major axis, ventricular perimeter length, ventricular volume, rate of change of ventricular volume (dV/dt), and shape index during the cardiac cycle.

throughout the cardiac cycle: the length of the ventricular major axis, the length of the cavity perimeter, the ventricular volume (derived using the area-length method¹⁴), the rate of change of volume, and a shape index. The shape index¹⁵ was calculated by the formula $4\pi(\text{area})/(\text{perimeter})^2$. It expresses how nearly the ventricular cavity outline in the plane being studied resembles a circle, which has a shape index with a value of one. Mitral valve opening was taken as occurring at the time of the frame immediately preceding the frame that first showed unopacified blood entering the left ventricle during diastole. A marker on the paper chart recorder that showed the onset of contrast injection allowed the high fidelity pressure trace for the beat being analysed to be identified. The pressure trace was digitised (200 Hz sampling frequency) and plots were generated to show pressure during the cardiac cycle and the rate of change of pressure (dP/dt) with time. The time constant (τ) of diastolic isovolumic left ventricular pressure decay was calculated from a plot of the natural log of pressure (P) with time, which assumes the pressure asymptote to be zero.¹⁶ The time at which left ventricular pressure reached a minimum value ($P_{\min}$) was taken as the point at which the plot of dP/dt reached the zero baseline in diastole.

Regional wall motion was studied by analysing the motion of 40 separate points equally spaced around the perimeter of the left ventricular cavity. We used established normal limits for the amplitude and

timing of wall motion to identify regional hypokinesia and asynchrony.¹⁷

The start of diastole was defined as the time of peak negative dP/dt and the end was taken to be the time of onset of the electrocardiographic Q wave of the following beat. The time of minimum left ventricular pressure was used to divide diastole into an early and a late phase. The following were measured:

(a) Left ventricular peak systolic pressure, end diastolic pressure, pressure at the time of mitral valve opening (P_{mvo}), and minimum pressure ($P_{\min}$).

(b) The time constant (τ) of left ventricular pressure decay during isovolumic relaxation.

(c) The maximum rate of change of pressure during pressure rise ($+dP/dt$) and pressure fall ($-dP/dt$).

(d) Left ventricular end diastolic volume (synchronous with the onset of the Q wave on the electrocardiogram), end systolic volume (minimum volume), and volume at $P_{\min}$.

(e) Left ventricular stroke volume and ejection fraction.

(f) The respective volumes entering the left ventricle during early diastole and late diastole expressed in absolute terms and as a percentage of the total stroke volume.

(g) The maximum rate of increase of left ventricular volume during diastole (peak dV/dt).

(h) Left ventricular shape index at end diastole, end systole, and at $P_{\min}$.

(i) The length of the left ventricular major axis at

Table 1 Pressure data

Patient		LVSP (mm Hg)	LVEDP (mm Hg)	$P_{\min}$ (mm Hg)	P_{mvo} (mm Hg)	$+dP/dt$ (mm Hg/s)	$-dP/dt$ (mm Hg/s)	τ (ms)
1	C	120	9	-3	18	1011	1222	44
	A	122	16	2	29	1039	982	57
2	C	129	12	5	10	1157	1093	44
	A	135	31	10	51	996	1169	60
3	C	115	28	3	31	863	884	50
	A	139	36	15	36	1002	996	82
4	C	154	19	6	47	1166	1308	38
	A	163	30	9	67	1309	1313	43
5	C	110	9	-4	18	1104	845	38
	A	125	13	-2	21	1130	1279	39
6	C	151	34	14	42	1072	1097	57
	A	150	36	14	52	1188	1251	58
7	C	108	26	0	34	829	907	54
	A	129	34	12	55	881	1066	64
8	C	174	27	12	52	1067	1164	62
	A	155	37	22	70	904	909	65
9	C	134	43	19	42	943	1013	79
	A	154	45	22	47	858	971	70
10	C	229	37	2	61	1722	2033	41
	A	239	55	20	56	2036	2671	44
11	C	166	17	-4	27	1396	1377	33
	A	156	20	12	39	1586	1254	43
Mean (SD)	C	144 (36)	24 (11)	5 (8)	35 (16)	1121 (253)	1177 (332)	49 (13)
	A	151 (32)	32 (12)	12 (8)	48 (15)	1175 (357)	1260 (489)	57 (14)
	p	NS	0.001	0.002	0.01	NS	NS	0.02

C, control; A, angina; LVSP, peak left ventricular systolic pressure; LVEDP, left ventricular end diastolic pressure; $P_{\min}$, minimum pressure; P_{mvo} , pressure at time of mitral valve opening; dP/dt , peak rate of change of left ventricular pressure; τ , time constant of pressure fall in early diastole.

end diastole, end systole, and at Pmin. This was defined as the distance from the mid point of the aortic root to the most distant point on the cavity perimeter.

(j) Time intervals: cycle length; Q - peak negative dP/dt; Q - mitral valve opening; Q - peak dV/dt; and Q - Pmin.

STATISTICAL METHODS

Results are expressed as mean (1 SD). Differences between means were compared by Student's paired *t* test. A *p* value of < 0.05 was regarded as significant.

Results

Figures 2 and 3 and tables 1-3 show the measurements made at rest and during angina of pressure and volume and the indices derived from them. Mean heart rate in the group was significantly higher during angina at the time of the second angiogram (72 (19) beats/min) than at rest (64 (11) beats/min) (*p* < 0.01). In three of the 11 patients (cases 3, 8, and 9) heart rate either decreased or was unchanged during angina.

PRESSURE DATA (TABLE 1)

Left ventricular peak systolic pressure was unchanged by angina but pressures were raised throughout the period of diastole. Left ventricular end diastolic pressure rose by 8 (6) mm Hg (*p* < 0.001) as did

minimum left ventricular pressure by 8 (6) mm Hg (*p* < 0.005). Left ventricular pressure at the time of mitral valve opening rose by 13 (12) mm Hg (*p* < 0.01). Peak dP/dt and peak negative dP/dt were unchanged by angina.

The time constant (τ) of pressure decay during isovolumic relaxation was 49 (13) ms at rest and increased to 57 (14) ms during angina (*p* < 0.02).

VOLUME DATA (TABLE 2)

The left ventricular end diastolic volume was unchanged by angina but there was a small though significant rise in minimum volume from 44 (17) ml at rest to 54 (18) ml during angina (*p* < 0.01). In consequence, the ejection fraction fell by 5 (6) % (*p* < 0.05). Changes in stroke volume were inconsistent, although there tended to be a fall with angina. The left ventricular volume at the time of minimum left ventricular pressure was 110 (34) ml at rest and 106 (30) ml with angina (NS). Figure 2 shows the relation between left ventricular pressure and volume at the time of minimum left ventricular pressure at rest and during angina in individual patients. In most patients at this moment in the cardiac cycle the pressure-volume point is moved upwards and sometimes leftwards during angina, indicating a higher intracavity pressure for a given volume. The upward movement was statistically significant, the lateral movement (that is volume change) was not. At rest the volume of blood entering

Table 2 Volume data

Patient		EDV (ml)	MV (ml)	EF (%)	SV (ml)	V _{min} (ml)	SVED (ml)	SVED (%)	SVLD (ml)	SVLD (%)	dV/dt (ml/s)
1	C	205	54	74	151	144	90	60	61	40	714
	A	200	48	76	152	130	82	54	70	46	743
2	C	103	19	82	84	71	48	57	36	43	453
	A	121	46	62	75	87	35	47	40	53	566
3	C	177	42	76	135	116	74	55	71	45	749
	A	205	60	71	145	119	59	41	86	57	698
4	C	139	51	63	88	95	44	50	44	50	507
	A	133	60	55	73	95	35	48	38	52	484
5	C	169	32	81	137	111	79	57	58	43	588
	A	174	46	74	128	96	50	39	78	61	648
6	C	227	85	63	142	181	96	68	46	32	740
	A	239	102	57	137	164	62	45	75	55	779
7	C	159	43	73	116	110	67	57	49	43	623
	A	166	47	72	119	109	62	52	57	48	710
8	C	204	36	82	168	137	106	63	62	37	756
	A	209	39	81	170	137	98	57	72	43	625
9	C	152	50	67	102	93	43	42	59	58	338
	A	159	64	60	95	104	40	42	55	58	536
10	C	143	42	71	101	94	52	51	49	49	627
	A	141	47	67	94	68	21	22	73	78	411
11	C	130	36	72	94	64	28	30	66	70	520
	A	121	35	71	86	63	28	33	58	67	632
Mean (SD)	C	164 (37)	44 (17)	73 (7)	120 (28)	110 (34)	66 (25)	54 (10)	55 (11)	46 (10)	601 (136)
	A	170 (39)	54 (18)	68 (8)	116 (33)	106 (30)	52 (24)	44 (10)	64 (15)	56 (10)	621 (112)
	<i>p</i>	NS	0.01	0.05	NS	NS	0.005	0.01	0.05	0.01	NS

C, control; A, angina; EDV, end diastolic volume; MV, minimum volume; EF, ejection fraction; SV, stroke volume; V_{min}, volume at time of minimum pressure; SVED, stroke volume entering left ventricle during early diastole; SVLD, stroke volume entering left ventricle during late diastole; dV/dt, peak rate of volume increase during diastole.

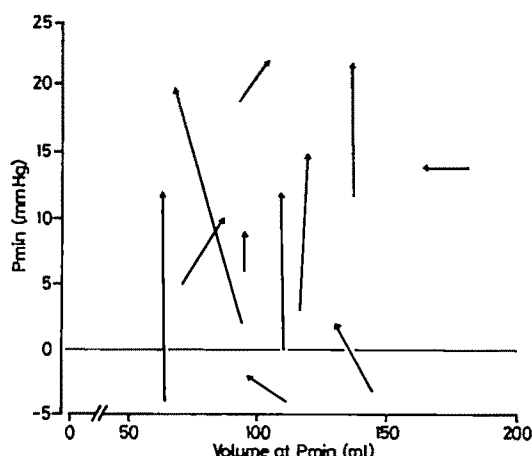


Fig 2 Left ventricular pressure-volume relations at the time of minimum left ventricular pressure. The arrows represent the change in this relation with an episode of angina in individual patients.

the left ventricle during early diastole was 66 (25) ml and during late diastole it was 55 (11) ml, comprising respectively 54 (10) % and 46 (10) % of the total stroke volume. Angina was associated with a significant fall in the volume of blood entering the left ventricle during early diastole when expressed either in absolute (14 (12) ml; $p < 0.005$) or percentage terms (10 (10) %, $p < 0.01$). In consequence, during angina, significantly more blood, either in absolute ($p < 0.05$) or percentage terms ($p < 0.01$) entered the left ventricle in late diastole than at rest. Despite the reduction in ventricular inflow volume during early diastole the peak rates of volume inflow were unchanged.

Figure 3 shows the pressure-volume relations for individual patients at rest and during angina at the time of P_{min} and at end diastole. During angina in 10 of the 11 patients there was an upward shift of the diastolic pressure-volume relation in this period of late diastole but, with the exception of patients 2 and 4, this shift was apparent at the start of late diastole and during late diastole no further divergence of the two relations was seen; in fact in three patients convergence of the relation was apparent. Thus in the group overall the rise in left ventricular end diastolic pressure induced by angina was virtually identical in magnitude with the rise in P_{min} , and yet, during the period of late diastole bounded by these two times, a proportionally greater volume of blood entered the left ventricle than in the resting state. The values for the ratio of the change in pressure to the change in volume during late diastole ($\Delta P/\Delta V$) are shown with each plot. $\Delta P/\Delta V$ calculated in this way measures ventricular stiffness during late diastole when filling

is passive. The mean $\Delta P/\Delta V$ for the 11 patients was 0.355 (0.16) mm Hg/ml at rest and 0.331 (0.147) mm Hg/ml during angina (NS).

LEFT VENTRICULAR GEOMETRY (TABLE 3)

The left ventricular end diastolic shape index was unchanged by angina. The shape index at minimum volume rose by 0.019 (0.019) ($p < 0.01$) during angina, indicating that the ischaemic ventricle was more spherical at end systole. There was also a trend for the shape index at the time of minimum pressure to increase with angina, but this was not statistically significant.

The lengths of the left ventricular major axis at end diastole and at the time of minimum volume were both significantly increased during angina ($p < 0.05$). At the time of minimum pressure the length of the major axis was similar at rest and during angina. When the length of the major axis at minimum pressure was expressed as a percentage of the total change in length during diastole, however, there was a significant reduction of 10 (9) % ($p < 0.01$) during angina. Thus angina is associated with the development of an abnormal pattern of ventricular diastolic shape change that is manifested by early assumption of a spherical configuration related to a delayed increase in the major axis of the ventricle.

TIME INTERVALS (TABLE 4)

The times of Q to peak negative dP/dt , Q to mitral valve opening, Q to peak rate of volume increase during diastole, and Q to minimum left ventricular pressure were all unchanged by angina. Figure 4 shows the mean for the time relations between peak negative dP/dt , mitral valve opening, peak rate of volume increase, and minimum left ventricular pressure at rest and during angina in the 11 patients. Angina did not significantly alter these time relations although there was an obvious shortening of the interval between peak rate of volume increase and minimum left ventricular pressure and lengthening of the interval between peak negative dP/dt and mitral valve opening, which approximates to the period of isovolumic relaxation. The duration of early diastolic filling (mitral valve opening to minimum left ventricular pressure) fell from 134 (47) ms at rest to 106 (46) ms during angina but this change was not significant either in absolute terms or when expressed as a percentage either of the total filling period or of the cardiac cycle.

EFFECT OF REGIONAL WALL MOTION ABNORMALITIES

Angina induced regional wall motion abnormalities in all of the patients. Nine patients developed regions of hypokinesis (mean number of affected segments

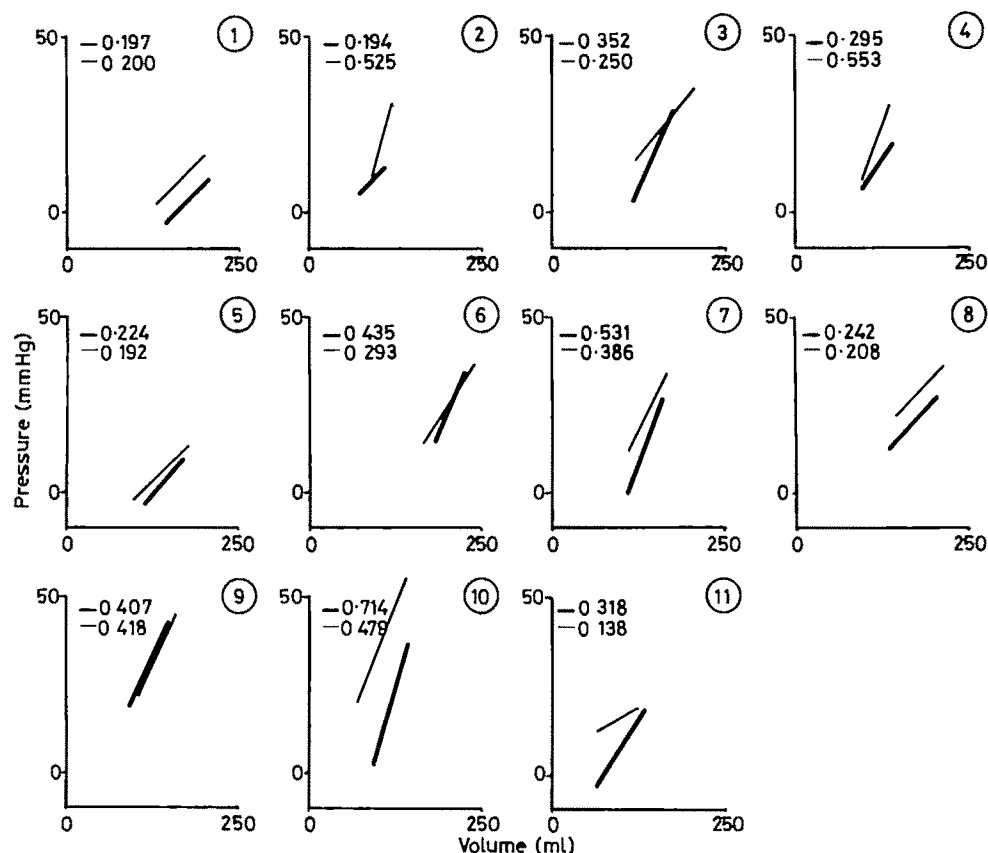


Fig 3 Pressure-volume relations during late diastole at control (bold lines) and during angina in 11 patients. For each plot, pressure (mm Hg) is on the ordinate and volume (ml) on the abscissa. The values displayed at the top left hand corner of each plot indicate the mean slope (mm Hg/ml) of the pressure volume relation during late diastole which is a measure of left ventricular chamber stiffness.

six, range 3–12). Seven patients developed regions of asynchrony (mean number of affected segments six, range 5–9), either in isolation (two cases) or in association with hypokinesia (five cases). There was no discernible relation between the presence or extent of either kind of regional wall motion abnormality and the development of, or the magnitude of, altered measurements of left ventricular early diastolic function including changes in left ventricular geometry.

Discussion

The purpose of this study was to investigate the effects of an attack of angina on events in early diastole. Early diastole was taken as the time between peak negative dP/dt and minimum left ventricular pressure. It thus included a period of isovolumic relaxation and most of the ventricular rapid filling

period, the time of peak inflow being recorded before minimum pressure. Left ventricular pressure decay during isovolumic relaxation is exponential, which means that its rate can be measured as a time constant.¹⁶ Minimum left ventricular pressure represents the point at which ventricular pressure and volume begin to increase together—that is to show simple passive behaviour—so that only from this time can the slope of the pressure-volume relation be used as a measure of ventricular cavity stiffness.

We found that an attack of angina consistently affected early diastole. As in previous studies,^{18,19} the time constant of the fall in left ventricular pressure was increased. A reduction in the rate of pressure fall would be predicted to prolong the periods of isovolumic relaxation and early diastole. However, this was not seen, probably because its effects were cancelled out by a simultaneous increase in ven-

Table 3 Left ventricular geometry

Patient		EDSI	MVSI	PminSI	EDL (cm)	MVL (cm)	PminL (cm)	PminL (%)
1	C	0.850	0.663	0.800	10	7.3	9.3	74
	A	0.850	0.688	0.850	10	7.0	8.4	47
2	C	0.884	0.675	0.850	8.1	5.6	7.0	58
	A	0.844	0.713	0.844	8.6	7.0	7.9	56
3	C	0.881	0.675	0.825	10	7.2	8.9	61
	A	0.875	0.713	0.831	10.4	7.7	9.0	48
4	C	0.784	0.575	0.750	9.2	7.5	8.4	53
	A	0.800	0.600	0.781	9.0	7.7	8.3	46
5	C	0.894	0.675	0.850	8.6	5.9	7.9	74
	A	0.894	0.650	0.844	8.9	7.5	8.2	50
6	C	0.875	0.725	0.856	10.5	8.9	9.6	44
	A	0.888	0.750	0.875	10.5	9.3	9.7	33
7	C	0.869	0.688	0.836	9.0	6.5	8.2	68
	A	0.881	0.700	0.863	9.2	6.6	8.1	58
8	C	0.805	0.438	0.715	10.2	8.7	9.2	33
	A	0.771	0.430	0.745	10.5	9.2	9.6	31
9	C	0.834	0.700	0.788	8.9	6.5	8.0	62
	A	0.844	0.725	0.825	9.1	6.8	7.9	48
10	C	0.813	0.594	0.744	9.4	7.7	8.4	41
	A	0.794	0.613	0.681	9.9	8.0	8.8	42
11	C	0.850	0.681	0.750	9.1	6.4	7.6	44
	A	0.831	0.713	0.781	8.9	6.2	7.4	44
Mean (SD)	C	0.849 (0.036)	0.644 (0.081)	0.797 (0.051)	9.4 (0.7)	7.1 (1.1)	8.4 (0.8)	56 (14)
	A	0.843 (0.041)	0.663 (0.090)	0.811 (0.058)	9.5 (0.7)	7.5 (1.0)	8.5 (0.7)	46 (8)
	p	NS	0.01	NS	0.05	0.05	NS	0.01

C, control; A, angina; EDSI, end diastolic shape index; MVSI, shape index at minimum volume; PminSI, shape index at time of minimum pressure; EDL, length of long axis at end diastole; MVL, length of long axis at minimum volume; PminL, length of long axis at time of minimum pressure.

tricular diastolic pressure, which has previously been shown to have a strong inverse correlation with isovolumic relaxation time.²⁰ Not only was the duration of early filling unaffected by angina but also the time relations between early diastolic events seemed unchanged although it should be borne in mind that the timing of mitral valve opening was derived from angiography and is thus liable to error because of the interval (20 ms) between cine frames. We were unable to detect any discernible relations between the time constant of pressure fall or the changes in the time constant induced by ischaemia and any other manifestation of left ventricle diastolic function.

In control conditions, we found that just over half the stroke volume entered the left ventricle before the time of minimum left ventricular pressure; this value was rather higher than that previously reported.^{21, 22} Angina consistently reduced this early diastolic inflow, both in relative and absolute terms; although

the duration of early diastole was not significantly reduced and the timing of minimum pressure in relation to peak inflow rate was maintained. As a corollary the proportion of stroke volume entering the left ventricle during late diastole was significantly increased. Angina increased ventricular cavity pressures throughout diastole; and the increases at the times of mitral valve opening, minimum pressure, and end diastole were statistically significant. Cavity geometry also changed; end systolic volume rose, the shape index indicated that the cavity was more spherical, and lengthening of the ventricular long axis during early diastole was delayed.

In the present study the heart rate during angina was on average eight beats/min higher than the resting value, raising the question of whether the changes we saw and ascribed to angina were in fact merely secondary to a rate change. An increase in heart rate is characteristically associated with shortening of the diastolic period. Inspection of our results clearly shows that it was the period of late diastole that was principally shortened. The duration of early diastole was unchanged by angina: 16.8% of the total cardiac cycle at control and 17.4% during angina. A combined analysis of our study patients at rest and a further 10 normal subjects studied in our laboratory showed that, over the range of heart rate found in our study, the duration of early diastole seems to have no consistent relation with cycle length ($r = 0.25$). Finally, in three of our patients (3, 8, and 9) cycle length either increased or was unchanged

Table 4 Mean (SD) time intervals (ms)

	Control	Angina
Cycle length	944 (161)*	829 (222)*
Q to peak negative dP/dt	413 (36)	398 (48)
Q to mitral valve opening (MVO)	438 (47)	436 (47)
Q to peak rate of volume increase (dV/dt)	524 (27)	515 (54)
Q to minimum ventricular pressure	572 (49)	542 (72)

* $p < 0.01$.

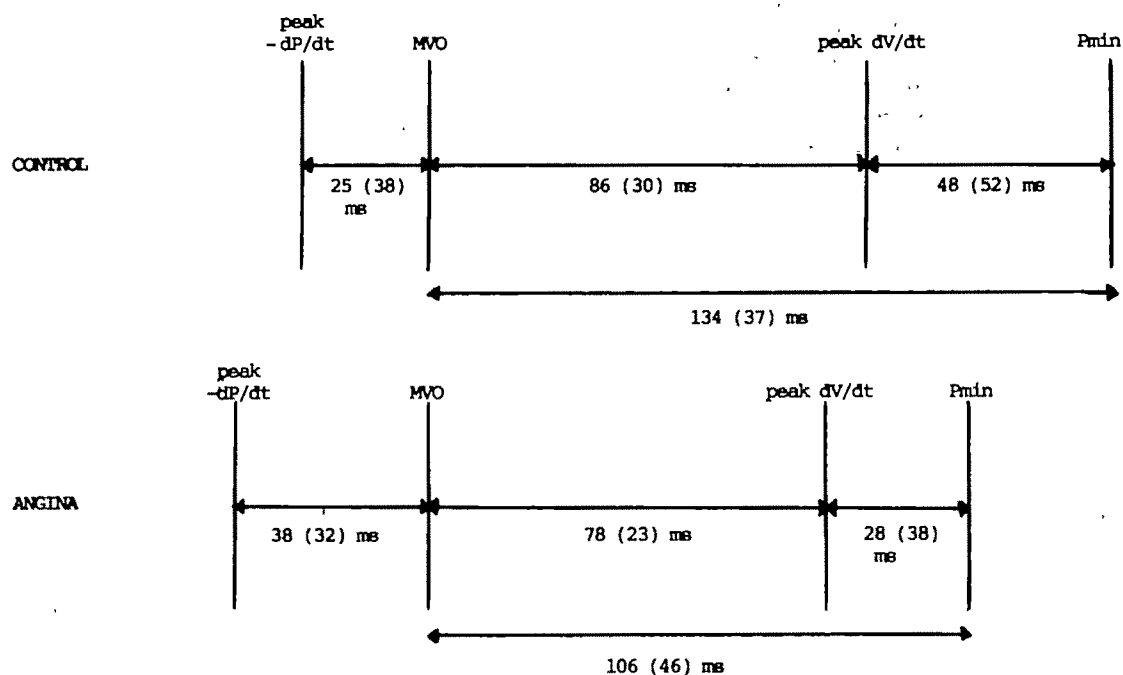


Fig 4 Schematic representation of time relations between peak negative dP/dt , mitral valve opening (MVO), peak rate of ventricular volume increase during diastole (dV/dt), and minimum left ventricular pressure (P_{min}) at control and during an episode of angina.

(± 20 ms) by angina. These three subjects showed changes resembling those in the other eight subjects in whom heart rate was increased during angina. We therefore conclude that angina directly modifies early as well as late diastolic function in patients with coronary artery disease.

An increase in ventricular end diastolic pressure and an upward shift of the pressure-volume curve are well recognised signs of an episode of myocardial ischaemia,¹² and they often precede both symptoms or electrocardiographic changes. When end diastolic pressure increases in the absence of significant changes in end diastolic volume, as was the case in our patients, it is often taken as evidence of an increase in myocardial stiffness. This feature has been variously ascribed to delayed deactivation of actin-myosin cross bridges⁹ or to increased myocardial turgor¹⁰ resulting from the increase in aortic pressure that often accompanies an anginal episode. However, cavity compliance and, still less, myocardial stiffness cannot be estimated from end diastolic values of pressure and volume alone. Myocardial compliance at any point during diastole is represented by the slope of the pressure-volume relation. In this study we used the simplest possible model and assumed that there was a linear relation between left ventricular pressure and volume over the range in which

both increased together during late diastole. We found that although an attack of angina caused an upward shift of the ventricular diastolic pressure-volume curve this was not associated with any consistent change in cavity stiffness assessed from the slope of the pressure-volume relation. This conclusion would not have been altered had we made use of the popular but unproved idea that the passive left ventricular pressure-volume curve is exponential. Shifting passive diastolic pressure-volume relations have been explained in several ways. Pericardial constraint⁷ is a possibility but this mechanism, which would have its predominant effect during late diastole, seems unlikely in our group of patients in whom during late diastole the left ventricle was operating over the same volume range during angina as at control. The left ventricular diastolic pressure-volume relation may be altered by changes in right ventricular shape, volume, or pressure, the effect being modulated by the pericardium or the shared interventricular septum.⁷ For the reasons described above, the pericardial constraint seems unlikely, but we cannot exclude the possibility that a hypothetical disturbance of right ventricular diastolic function contributed to the shift of the pressure-volume relation found in our patients.

The characteristic pattern of falling pressure and

increasing volume in early diastole has been recognised for many years.²³ In human beings it has been detected on simultaneous M mode echocardiograms and pressure measurements²⁴ and more recently by angiography.²¹ This behaviour departs widely from any simple passive model, and its mechanism is still uncertain. It has been suggested that it is the result of decay in the active state being prolonged beyond mitral valve opening²⁵ so that the fall in active wall tension induced by myocardial relaxation outweighs the increase in passive tension caused by the rise in cavity volume. The time of minimum pressure thus represents equilibrium between these two processes. This explanation thus requires that an episode of angina, which prolongs relaxation, would also delay the time of minimum pressure. But we did not see this in our patients.

The phenomenon of falling pressure associated with rising volume has also been ascribed to the effects of restoring forces (that is to elastic recoil). These forces reside in connective tissue elements within the myocardium. They are energised during systole and then act during diastole to return the ventricle to its pre-contractile configuration.³⁴ Their extent is thus likely to be proportional to the distortion of cavity geometry and volume at end systole. Not until pressure and volume start to rise together—that is at the time of minimum cavity volume—are their effects outweighed by the passive mechanical properties of the ventricular myocardium. Our results can readily be explained by these ideas. The changes in end systolic volume and shape index are exactly those expected to reduce the forces that restore tension—thus increasing early diastolic pressure and reducing the early diastolic inflow of blood. Asynchronous onset of outward wall motion, commonly seen in angina, may also dissipate these forces and so exacerbate the disturbance. The peak filling rate was little changed by angina; in the face of increased early diastolic ventricular pressure it could only have been maintained by an increase in early diastolic left atrial pressure which would have maintained the corresponding atrioventricular pressure difference.²⁶

A normal ejection fraction and a low end systolic volume depend on the presence of longitudinally as well as circumferentially arrayed myocardial fibres.²⁷ Whereas circumferential fibres are largely to be found in the mid-wall region, most longitudinally orientated fibres are found subendocardially²⁸ and are thus particularly susceptible to the effects of ischaemia. The delay in left ventricular long axis lengthening during early diastole that we saw in our patients is thus a predictable consequence of an attack of angina.

This study illustrates the complex nature of distur-

bed left ventricular diastolic function during angina. The upward displacement of the diastolic pressure-volume relation, so often attributed to increased myocardial stiffness, appears as the direct consequence of abnormal early diastolic events. Our results may also have therapeutic relevance. Anti-anginal drugs often have vasodilator activity. Since such drugs allow end systolic volume to become normal, and since diastolic disturbances are such an important component of the clinical syndrome of angina, it might even be that the mechanisms described here, rather than coronary vasodilatation or reduced systolic wall stress underlie their therapeutic action. Further work is needed to settle these important questions.

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The effects of treatment with felodipine as a single agent in coronary artery disease

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SUMMARY In an earlier study one dose of the vasodilator felodipine improved haemodynamic function in patients with angina without having a negative inotropic effect. The haemodynamic response of sustained treatment with felodipine as a single agent in stable angina was investigated in a double blind crossover study of 25 patients. The dosage of felodipine was increased from 5 mg twice daily to 10 mg twice daily after two weeks. Twenty one patients completed the study, two were withdrawn because of acute myocardial infarction, and a further two because of symptoms of vasodilatation. Felodipine reduced both supine and erect blood pressure and increased the resting heart rate. Median exercise time was increased by 10% at two weeks and 7% at four weeks. There was a sustained reduction in the number of angina attacks and use of sublingual nitrate on active treatment.

Felodipine has antianginal effects but these are limited and seem less than those of other related compounds. This finding is unexpected and possibly related to increased heart rate.

Felodipine, a dihydropyridine, is a new vasodilating agent which reduces blood pressure, increases stroke volume, and in a single dose study increased exercise capacity.¹ It has also been shown to be a useful adjunctive agent to β blockade in stable angina.² To investigate the potential beneficial effects of longer term treatment we studied the effects of an increasing dose of felodipine on exercise tolerance, symptoms, and the haemodynamic response to exercise.

Patients and methods

We studied 25 patients (17 men and eight women, aged 40-65 years (mean 52.0)) who had had stable angina for at least two months with at least five attacks per week. All patients had an initial positive exercise test with at least 1 mm of ST depression associated with chest pain. They gave their informed consent to the study. Fertile women were excluded. We also excluded patients with important valve disease, myocardial infarction within the past two months, unstable angina, systolic blood pressure < 100 mm Hg, insulin dependent diabetes, a history of severe allergic response, or severe hepatic failure.

All medication other than sublingual nitrates was stopped for at least two weeks before the start of the study. Seven patients had already been treated with nifedipine and three with atenolol.

The study had three parts—a run in period of two weeks on placebo followed by two double blind crossover periods of four weeks on felodipine or placebo. After two weeks we increased the dose of either felodipine or placebo from 5 mg twice a day to 10 mg twice a day if no adverse features had occurred. The tablets taken during the felodipine and placebo treatment periods were dispensed in computer generated random order. After the first and second two week periods the patients performed a symptom limited Bruce protocol exercise test and had a clinical examination with history. The erect and supine blood pressure and pulse were carefully recorded. All exercise tests were performed between 1 and 3 hours after the last dose of the study medication. Plasma samples were taken for felodipine analysis at each visit during the crossover period.

At each visit the patients were given a diary card to record the number of angina attacks and consumption of sublingual nitrate. At the end of the study the patients returned to their usual medication.

Results are expressed as median or mean and were analysed by Wilcoxon matched pairs signed ranks test and Student's *t* test; a probability value of < 0.05 was regarded as statistically significant.

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Results

Twenty one patients completed the study. Of the four patients who were withdrawn from the study: one experienced severe abdominal pain while on placebo, one complained of flushing and burning of her feet, legs, and face while taking felodipine, and an acute myocardial infarction developed while two patients were taking felodipine 5 mg twice daily. After two weeks' treatment, 11 patients had their dosage increased from 5 mg twice daily to 10 mg twice daily but in one patient the dose was subsequently reduced because minor side effects of vasodilatation developed.

At the end of the double blind periods 11 patients were taking felodipine 5 mg twice daily, 10 patients were taking 10 mg twice daily, and 10 and 11 patients were taking 5 mg and 10 mg of placebo respectively. Plasma analysis showed that two additional patients had appreciable concentrations of plasma felodipine when they should have been taking placebo. We excluded their data from subsequent analysis. Data from the remaining 19 patients were analysed.

Supine and erect blood pressure were lower during felodipine treatment than during placebo treatment. The mean reductions after two weeks' treatment with felodipine were 8/7 mm Hg ($p < 0.01$) and 8/4 mm Hg ($p < 0.05/NS$) respectively. The corresponding figures after four weeks' treatment were 3/5 mm Hg ($NS/p < 0.05$) and 7/6 mm Hg ($p < 0.05/NS$). After four weeks of felodipine treatment the mean heart rate in supine patients increased slightly (6 beats/min ($p < 0.05$)). After two weeks of felodipine treatment the median duration of exercise was 10% higher than during placebo treatment ($p < 0.05$). The increase (7%) after four weeks was not statistically significant (table 1). When patients were taking felodipine 5 mg twice a day the mean (SD) heart rate at maximal exercise was increased by seven beats per minute (from 144 (12) to 151 (13) NS),

systolic blood pressure was reduced from 165 (19) to 159 (19) mm Hg (NS), and the mean (SD) rate-pressure product was essentially unchanged (from 24500 (3700) to 23900 (3300)). When patients were taking felodipine 10 mg twice a day, the mean (SD) heart rate increased from 149 (14) to 150 (14), the systolic blood pressure was reduced from 158 (15) to 154 (18) mm Hg (NS), and the rate-pressure product was again essentially unchanged (from 23700 (3100) to 23400 (3300)). We did not find a significant relation between ST depression and the rate-pressure product at maximal exertion, although median ST depression was reduced after two weeks' treatment with felodipine (2 to 1.8 mm, $p < 0.05$) but not after four weeks.

The diary cards showed a sustained tendency towards fewer angina attacks and reduced consumption of glyceryl trinitrate during treatment with felodipine (NS) (tables 2 and 3). Both systolic and diastolic blood pressure fell significantly after exercise, particularly at 10 minutes (8/7 mm Hg, $p < 0.01/p < 0.05$). The heart rate was also significantly increased after exercise, especially after four weeks' treatment with felodipine (at 10 minutes it was 11 beats per minute higher ($p < 0.001$)). No clinically significant differences in mean body weight, angle circumference, or haematological or biochemical values were noted.

Discussion

The efficacy of calcium antagonist vasodilator agents in treating symptomatic coronary artery disease is well established both on their own and in combination with other agents such as β blockers. Most of these agents have negative inotropic effects, which can limit their usefulness; none the less, felodipine has been shown to increase cardiac output^{3,4} and to increase resting myocardial blood flow.³ Interest has therefore been expressed in establishing its potential

Table 1 Exercise duration(s) in different treatment groups

	Placebo after 2 weeks		Felodipine after 2 weeks	Placebo after 4 weeks		Felodipine after 4 weeks
<i>Felodipine 5 mg twice a day at 2 and 4 weeks</i>						
n	11		11	11		11
Mean (SD)	514 (148)		558 (127)	556 (131)		588 (148)
Median	505	NS	586	540	NS	595
<i>Felodipine 5 mg twice a day at 2 weeks and 10 mg twice a day at 4 weeks</i>						
n	8		8	8		8
Mean (SD)	510 (176)		574 (141)	537 (163)		545 (123)
Median	528	NS	584	538	NS	530
<i>Totals</i>						
n	19		19	19		19
Mean (SD)	524 (157)		565 (134)	548 (145)		570 (140)
Median	505	$p < 0.05$	586	540	NS	568

Table 2 Number of angina attacks per week in different treatment groups

	Placebo after 2 weeks		Felodipine after 2 weeks	Placebo after 4 weeks		Felodipine after 4 weeks
<i>Felodipine 5 mg twice a day at 2 and 4 weeks</i>						
n	11		11	10		10
Mean (SD)	2.8 (1.9)		2.2 (3.2)	5.6 (6.4)		2.2 (3.0)
Median	2.7	NS	1.0	2.2	NS	0.8
<i>Felodipine 5 mg twice a day at 2 weeks and 10 mg twice a day at 4 weeks</i>						
n	8		8	8		8
Mean (SD)	6.2 (8.2)		5.2 (3.5)	5.3 (5.1)		3.2 (2.6)
Median	3.0	NS	4.8	4.8	NS	2.3
<i>Totals</i>						
n	19		19	18		18
Mean (SD)	4.2 (5.8)		3.4 (3.6)	5.0 (5.7)		2.8 (2.9)
Median	2.7	NS	2.0	2.9	NS	1.4

for treating patients with coronary artery disease.

Single doses of felodipine increased maximal cardiac output by 20% and the maximal pressure-rate product by 13%.¹ The relation between ST segment depression and the rate-pressure product during exercise was also favourably influenced. In a further study in which felodipine was added to conventional β blockade there was a significant improvement in exercise tolerance and daily attacks of angina.²

In our study although there was a similar improvement in exercise tolerance after two weeks' treatment, at four weeks the benefit was less apparent. This reduced benefit is not entirely unexpected because felodipine, in common with other peripheral vasodilators, induces reflex sympathetic activity thereby increasing heart rate and myocardial oxygen consumption, with a consequent effect on the drug's antianginal action. Both supine and erect blood pressure fell significantly as would be expected with a drug causing peripheral arteriolar vasodilatation.

Despite the increase in dosage in eight (42%) of the 19 patients at four weeks the effect of felodipine on mean exercise capacity was not as strong as at two

weeks. There are two possible explanations for this. Firstly a ceiling may have been reached at a dose of 5 mg twice a day, which suggests that the drug may have a flat dose response curve. This explanation is supported by the apparent lack of additional effect on the resting supine and erect blood pressure, median ST depression, and rate-pressure product at maximal exercise after increasing the dosage to 10 mg twice a day. Secondly, the training effect of repeated exercise tests could improve the results of both treatment groups; however, as the baseline exercise tolerance improves, the statistical significance of the measured improvement is reduced. As only 42% of the patients had their felodipine increased to 10 mg twice a day, subgroup analysis of patients taking 5 mg and 10 mg twice a day after 4 weeks has to be interpreted with caution in view of the relatively small numbers. Although an increase in the dosage of felodipine from 5 mg to 10 mg twice daily did not improve exercise tolerance or the rate-pressure product at maximal exercise, the number of weekly angina attacks was halved. The number of side effects reported was low and related to the vasodilatory properties of the drug.

Table 3 Use of sublingual glyceryl trinitrate in different treatment groups (tablets (0.5 mg) per week)

	Placebo after 2 weeks		Felodipine after 2 weeks	Placebo after 4 weeks		Felodipine after 4 weeks
<i>Felodipine 5 mg twice a day at 2 and 4 weeks</i>						
n	11		11	10		10
Mean (SD)	2.4 (2.7)		0.7 (0.8)	2.0 (2.0)		0.8 (1.4)
Median	1.5	p = 0.01	0.5	1.0	NS	0.0
<i>Felodipine 5 mg twice a day at 2 weeks and 10 mg twice a day at 4 weeks</i>						
n	8		8	8		8
Mean (SD)	4.8 (6.9)		3.1 (2.6)	4.0 (3.6)		2.1 (2.4)
Median	2.5	NS	3.5	3.8	NS	1.3
<i>Totals</i>						
n	19		19	18		18
Mean (SD)	3.0 (4.9)		1.7 (2.1)	2.9 (3.0)		1.4 (2.0)
Median	2.0	NS	0.5	1.6	p < 0.05	0.9

The first patient who experienced a myocardial infarction while taking felodipine had a poor initial exercise tolerance of 207 seconds and approximately three attacks of angina per day associated with exercise. During felodipine treatment exercise tolerance fell to 190 seconds and the number of anginal attacks increased by 16%. It is possible that in this patient the drug contributed to the development of these adverse features because it resulted in unopposed reflex sympathetic activity (thereby increasing myocardial oxygen consumption² or because it induced a coronary artery steal phenomenon. When it is used alone, nifedipine (a related dihydropyridine) can induce angina; the mechanism for this effect is not known.⁴ The second patient with a myocardial infarction had satisfactory initial exercise tolerance and approximately one anginal attack per week. Because he improved substantially on felodipine the development of infarction was unexpected, and it seems unlikely that it was related to the drug. This study shows that felodipine has anti-anginal properties in patients with coronary artery disease but these seem to be limited and less than those of other reported compounds such as nifedipine.^{6,7} It may be especially suitable for patients with angina and hypertension in whom its ability to maintain or increase the cardiac output is an advantage.^{4,8}

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Coronary angioplasty and left ventricular function in single vessel coronary artery disease

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SUMMARY Left ventricular function was investigated in 86 patients with single vessel coronary artery disease before and three to six months after successful angioplasty. Before angioplasty thallium-201 perfusion scintigraphy and technetium-99m gated equilibrium ventriculography in most patients showed that stress testing (exercise and ice water stimulation and isometric handgrip respectively) induced myocardial perfusion defects that were associated with a mean (SD) drop in left ventricular ejection fraction from 64 (6) % to 56 (7)%. After angioplasty there was residual coronary stenosis of $\leq 20\%$ of the diameter of the vessel in 78 patients (group 1) and of between 20 and 50% in eight patients (group 2). After the procedure the perfusion defects seen during stress resolved in 86% of group 1 and in 87% of group 2. Despite the apparent improvement in myocardial perfusion left ventricular dysfunction persisted in group 2—that is during stress the left ventricular ejection fraction fell from 65% (6) to 56% (5). In group 1, on the other hand, the improvement in myocardial perfusion was associated with significant improvement in left ventricular function with a normal increase in ejection fraction from 63 (5) at rest to 67 (6) during stress. Radionuclide studies, one to six weeks after angioplasty in 30 group 1 patients showed continuing left ventricular decompensation during stress in nine (30%) of them despite correction of perfusion defects. But reinvestigation three to six months after the procedure showed recovery of left ventricular function with an increase in ejection fraction from 66 (5) at rest to 69 (7) during stress.

These data indicate that coronary angioplasty procedures that give a residual stenosis of $\leq 20\%$ improve myocardial perfusion and the response of the left ventricle to stress. The functional improvement may be delayed for up to three months, however, possibly because arterial healing at the angioplasty site is delayed. On the other hand, when the residual stenosis is between 21 and 50% of the diameter of the vessel subclinical left ventricular dysfunction during stress may persist indefinitely.

Percutaneous transluminal coronary angioplasty effectively dilates diseased coronary arteries and in most cases leads to symptomatic relief and improved myocardial perfusion as judged by thallium-201 scintigraphy.¹ The effects of coronary angioplasty on left ventricular contractile function, however, are variable and although some improvement in the

response of ejection fraction to exercise can often be shown, in many patients a dyskinetic left ventricular contraction pattern persists after a successful procedure.^{1,2} The cause is unknown but continuing subclinical myocardial ischaemia is the most plausible explanation. To investigate further the effects of successful coronary angioplasty on left ventricular perfusion and contractile function, we performed radionuclide studies on 86 patients before angioplasty, soon after angioplasty, and between three and six months afterwards. This provided new information on the evolution of myocardial recovery after a successful procedure. We paid particular attention to the effect of residual stenosis on left ventricular performance.

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Patients and methods

PATIENTS

Of 95 patients originally considered for inclusion in the study, 86 underwent successful angioplasty; they form the basis of this report. There were 72 men and 14 women aged 29 to 66 years (mean (SD) 53 (9)). All had stable symptomatic single vessel coronary artery disease of the left anterior descending ($n = 49$), circumflex ($n = 18$), or right coronary arteries ($n = 19$). Resting left ventricular function was normal or near normal in every case although in 21 of the 29 patients with a history of previous myocardial infarction left ventriculography showed limited regional hypokinesis. Patients with akinetic myocardial segments, cardiomyopathy, or valvar heart disease were excluded. We also excluded patients with musculoskeletal disorders, intermittent claudication, and other non-cardiac disorders that prevented adequate exercise.

Coronary angioplasty

Angioplasty was carried out as previously described by Sowton *et al.*³ Criteria for a successful procedure included a residual coronary stenosis of $\leq 50\%$ the transluminal diameter and completion of the procedure without serious complications (myocardial infarction, referral for urgent bypass surgery, death). A 12 lead electrocardiogram was obtained before angioplasty, again immediately afterwards, and daily thereafter for three days. Electrocardiographic data together with daily measurements of plasma concentrations of creatine kinase excluded myocardial infarction in every patient. Before angioplasty patients were treated with nitrates, β blockers, and calcium antagonists. After the procedure β blockers were stopped (except in 19 hypertensive patients). Treatment with isosorbide mononitrate 20 mg twice daily, nifedipine slow release 20 mg twice daily, and aspirin 300 mg daily was continued. The luminal diameter of the coronary artery (in identical radiographic projections before and after coronary angioplasty) was measured by precision callipers. The degree of stenosis was expressed as a percentage of the diameter of the immediately adjacent normal artery.

NON-INVASIVE IMAGING

In every patient thallium-201 myocardial perfusion scintigraphy during exercise and technetium-99m gated equilibrium ventriculography were performed before angioplasty (within four weeks of the procedure) and again three to six months afterwards. In 30 patients (all with a residual stenosis of $\leq 20\%$ radionuclide imaging was performed early (< 6 weeks) after coronary angioplasty so that the

recovery of the left ventricle could be examined. In each patient studies of myocardial perfusion and ventriculography were carried out on the same day. Imaging was performed at least three hours after eating. In all patients, except those who were hypertensive, β blockers were stopped for 46–72 hours before the radionuclide studies; all other medication was continued. The images were interpreted by three independent observers.

Before thallium-201 tomography patients were exercised in the erect position on a bicycle ergometer at workloads that increased 25 W every two minutes. The exercise tests were maximal and symptom limited. Endpoints were: horizontal or downsloping ST segment depression ≥ 3 mm, angina of increasing severity, a drop in systolic blood pressure ≥ 20 mm Hg with progressive exercise, or significant rhythm disturbances. At peak exercise 60–80 MBq of thallium-201 was injected via an antecubital vein and the patient continued to exercise for a further minute at a lower workload. Myocardial imaging was started five minutes after the isotope injection and was repeated after three hours to assess redistribution. The patients lay supine beneath a gamma camera with a large field of view and a seven-pin-hole collimator. Images were recorded in a 128×128 matrix and reconstructed in the long axis of the heart in seven slices. We analysed four tomographic slices from apex to base of the left ventricle. Semiquantitative curves showing regional uptake for each patient in 10° segments were displayed in polar coordinates that were normalised to the area of maximum activity. Washout curves were constructed by plotting the absolute counts for exercise images and delayed images. These quantitative data were used to assist interpretation of the image.

Technetium-99m gated equilibrium ventriculography with in vitro labelling of red blood cells (^{99m}Tc , 500–800 MBq) was performed after the completion of the thallium-201 study. Images were recorded for 10 minutes in the anterior view and in the modified (caudal tilt) left anterior oblique 45° view that gave the best image of the left ventricular septum. A general purpose parallel hole collimator was used with a gamma camera with a small field of view. Stress was applied as ice water stimulation for five minutes followed by isometric handgrip for five minutes during which images were recorded in the modified left anterior oblique 45° position. Cardiac gating was triggered by the R wave of the electrocardiogram and the information was stored in 18 frames throughout the cardiac cycle, in a 64×64 matrix. The 18 frames were displayed in cine mode for the evaluation of regional abnormalities of wall motion. The left ventricular ejection fraction in the modified left anterior oblique 45° view was calculated by a

semiautomated method for defining the left ventricular area of interest, with automatic selection of background. Regional abnormalities of wall motion were assessed visually.

STATISTICAL ANALYSES

Comparisons of proportions were by χ^2 or Fisher's exact tests, as appropriate. Differences between groups were assessed by Student's *t* test.

Results

The 86 patients underwent successful angioplasty with a mean (1 SD) reduction in coronary artery stenosis from 89 (10) of the coronary artery diameter to 24 (9). The patients were divided into two groups for later analysis. Group 1 was 78 patients in whom the residual stenosis was $\leq 20\%$ (average 13 (7)%) and group 2 was eight patients in whom the residual stenosis was 21–50% (average 38 (7)%). Table 1 shows the effects of coronary angioplasty on the severity of stenosis and gradient, exercise haemodynamic function and performance, and left ventricular wall motion and perfusion during exercise. Figure 1 shows the functional responses, both global and regional, of wall motion to stress after angioplasty.

GROUP 1 ($\leq 20\%$ RESIDUAL STENOSIS)

Coronary angioplasty produced complete symptomatic relief in 90% of group 1, and this was

Table 1 Results of percutaneous transluminal coronary angioplasty (PTCA) in groups 1 and 2

	Group 1 (n = 78)		Group 2 (n = 8)	
	Before PTCA	After PTCA	Before PTCA	After PTCA
Age (yr)	54 (9)		52 (8)	
Dilatations (n)	6 (2)		7 (3)	
Stenosis (%)	86 (10)	13 (7)***	93 (10)	38 (7)***
Gradient (mm Hg)	59 (18)	9 (8)***	58 (23)	11 (13)***
Total work (W.min)	545 (254)	698 (285)***	616 (251)	740 (363)
Rest HR (beats/min)	71 (12)	70 (10)	80 (21)	73 (15)
Rest DP ($\times 10^3$)	9 (2)	9 (2)	10 (3)	9 (2)
Maximal HR (beats/min)	141 (21)	155 (21)***	147 (19)	156 (21)
Maximal DP ($\times 10^3$)	23 (5)	27 (6)***	24 (4)	27 (8)
Effort angina (n)	78	8***	8	0***
Ex perf defects (n)	78	9***	8	2**
Rest RWA (n)	19	5**	3	2
Stress RWA (n)	64	9***	7	7
Stress L.V dilat (n)	78	11***	8	7

p < 0.01, *p < 0.001 for difference compared with value before angioplasty. HR, heart rate; DP, double product; Ex perf, exercise perfusion; RWA, regional wall motion abnormality; L.V dilat, global left ventricular dilatation.

reflected by an increase in peak workload during bicycle ergometry from 545 (254) to 698 (285) Watt.minutes (p < 0.001).

Before angioplasty thallium-201 scintigraphy during exercise showed fully or partially reversible perfusion defects in 73 patients and irreversible

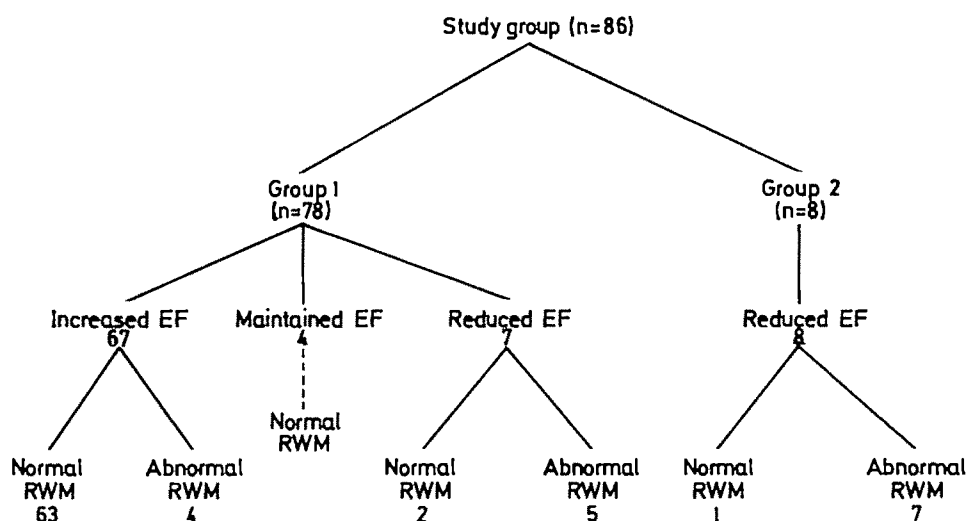


Fig 1 Effects of coronary angioplasty on the left ventricular response to exercise. Data for group 1 (residual stenosis $\leq 20\%$) and group 2 (residual stenosis $> 20\%$) are shown. EF, left ventricular ejection fraction; RWM, regional wall motion.

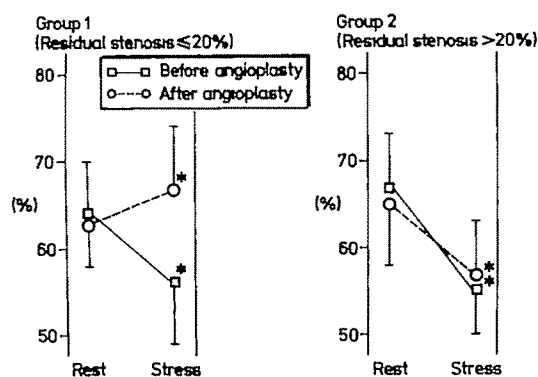


Fig 2 Effect of coronary angioplasty left ventricular ejection fraction during exercise and at rest in groups 1 and 2. * $p < 0.001$ compared with resting values.

defects in five patients. After angioplasty myocardial perfusion became normal in 69 (88%) patients, but in the remaining nine patients perfusion abnormalities persisted in the territory of the dilated artery.

Radionuclide ventriculography before coronary angioplasty showed stress induced left ventricular decompensation in all patients, with a rise in systolic and diastolic cavity dimensions and reduction in ejection fraction from 64 (6)% at rest to 56 (7)% during stress ($p < 0.001$, fig 2). After coronary angioplasty there was an improvement in the response of the left ventricle. Improvement was delayed, however, in nine out of 30 patients (subgroup 1b) who were studied within six weeks of angioplasty (fig 3). Despite successful coronary angioplasty these nine patients showed persistent stress induced increases in the dimensions of the left ventricular cavity (table 2) associated with reductions in ejection fraction from 61 (9)% at rest to 52 (9)% ($p < 0.05$) at peak exercise. Nevertheless, when these nine patients were restudied three to six months after the angioplasty a delayed recovery of left ventricular function was shown by increases in ejection fraction from 66 (5) to 69 (7)% ($p < 0.01$) at peak exercise (fig 4). Thus six months after coronary angioplasty group 1 showed an overall improvement

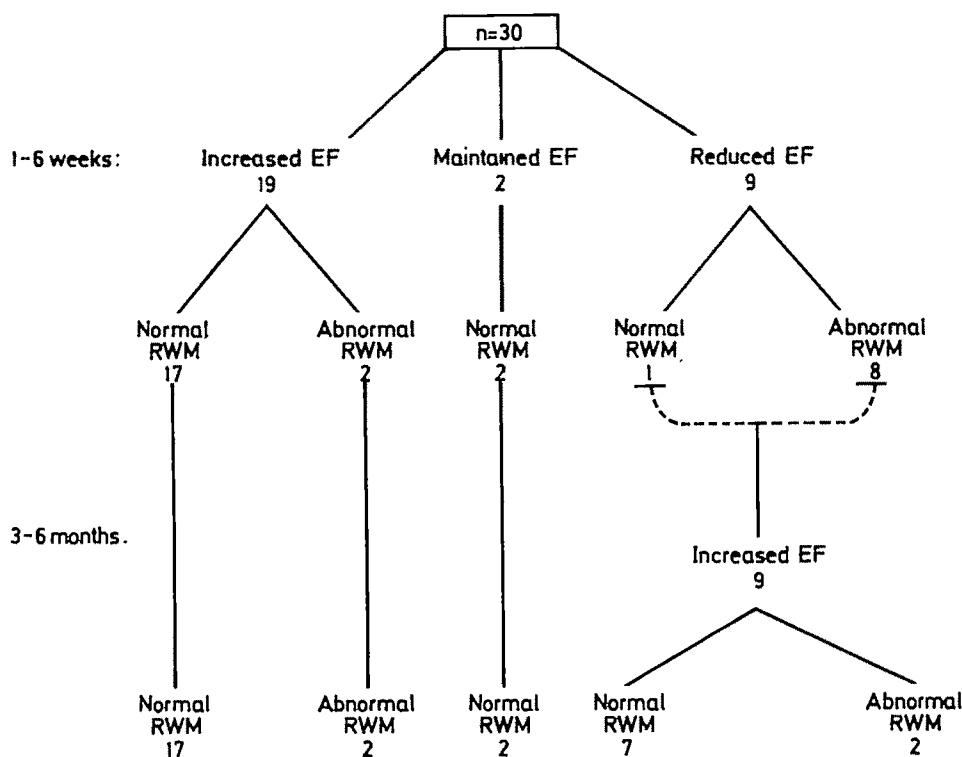


Fig 3 Results of early (1-6 weeks) and late (3-6 months) radionuclide ventriculography after successful coronary angioplasty in 30 patients all of whom had a residual stenosis $\leq 20\%$ (group 1). Note that in nine cases (subgroup 1b) recovery of left ventricular function was delayed. EF, ejection fraction; RWM, regional wall motion.

Table 2 Results of percutaneous transluminal coronary angioplasty (PTCA) in nine patients with $\leq 20\%$ residual stenosis and delayed left ventricular recovery

	Before PTCA	1-6 weeks after PTCA	3-6 months after PTCA
Age (yr)	55 (6)		
Dilatations (n)	5 (1)		
Stenosis (%)	83 (9)	10 (7)***	
Gradient (mm Hg)	67 (19)	8 (8)***	
Total work (W min)	492 (141)	600 (136)*	631 (129)**
Rest HR (beats/min)	75 (16)	74 (11)	74 (16)
Rest DP ($\times 10^3$)	9 (2)	9 (2)	9 (2)
Maximal HR (beats/min)	145 (22)	155 (17)*	158 (16)*
Maximal DP ($\times 10^3$)	25 (7)	27 (4)	28 (4)
Effort angina (n)	9	0***	0***
Ex perf defects (n)	9	1***	1***
Rest RWA (n)	2	2	1
Stress RWA (n)	9	7	0***
Stress LV dilat (n)	9	9	1***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ for difference compared with value before angioplasty. HR, heart rate; DP, double product; Ex perf, exercise perfusion; RWA, regional wall motion abnormality; LV dilat, global left ventricular dilatation.

in left ventricular function. Only seven of the patients (9%) showed persistent stress induced reductions in left ventricular ejection fraction, and for the whole group the mean ejection fraction increased from 63 (5)% at rest to 67 (6)% at peak exercise ($p < 0.001$).

Before angioplasty 64 patients had stress induced regional abnormalities of wall motion. After the procedure these tended to disappear in association with the overall improvement in left ventricular function. In patients with continuing stress related left ventricular decompensation, however, regional abnormalities of wall motion usually persisted. In seven of the nine patients who showed delayed recovery of left ventricular function the disappearance of regional abnormalities was also delayed.

GROUP 2 ($> 20\%$ RESIDUAL STENOSIS)

Coronary angioplasty produced complete symptomatic relief in all eight patients and an increase in peak workload during bicycle ergometry from 616 (251) to 740 (363) W.min ($p = \text{NS}$).

Before angioplasty thallium-201 scintigraphy during exercise showed reversible myocardial perfusion defects in every patient, but after the procedure the defects disappeared in six patients. Despite the improvement in myocardial perfusion, radionuclide ventriculography remained persistently abnormal three to six months after coronary angioplasty with stress induced increase in ventricular volume associated with reductions in ejection fraction (65 (6)% at rest to 56 (5)% during stress, $p < 0.01$). Seven of the patients showed persistent regional abnormalities of wall motion.

Discussion

The findings in this study show that successful coronary angioplasty with a residual stenosis $< 50\%$ of the luminal diameter of the coronary artery gives early relief of angina in most patients. The improvement in symptoms was associated with a restoration of regional myocardial perfusion as assessed by thallium-201 perfusion scintigraphy. Nevertheless subclinical stress induced left ventricular dysfunction during gated radionuclide ventriculography often persisted unless the coronary artery was widely patent with a residual stenosis of $\leq 20\%$. In some patients with wide coronary patency, however, left ventricular function was not fully recovered for up to three months. This suggests that restoration of normal perfusion is sometimes delayed until healing at the angioplasty site is complete.

The efficacy of coronary angioplasty for treatment of angina is well established.¹⁻³ In the present series more than 90% of the patients obtained early relief of symptoms. Despite the clinical efficacy of coronary angioplasty, beneficial effects on left ventricular function are more difficult to demonstrate—particularly in patients with multivessel disease.¹ All the patients in the present study, however, had single vessel coronary artery disease with well preserved left ventricular function before angioplasty. None had akinetic myocardial segments visible on the left ventricular contrast angiogram. These patients, therefore, were an appropriate group in which to evaluate the effects of coronary angioplasty on

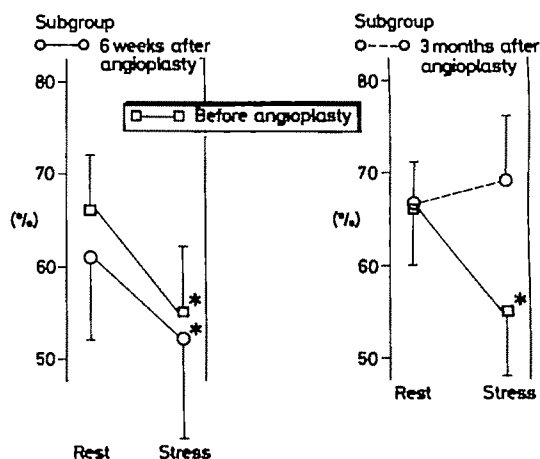


Fig 4 Left ventricular ejection fraction at rest and in response to stress before angioplasty and at 1-6 weeks and 3-6 months after angioplasty in nine group 1 patients with delayed recovery. * $p < 0.01$ compared with resting values.

regional myocardial ischaemia and left ventricular function.

Our finding of early correction of defects in the perfusion of thallium-201 after successful coronary angioplasty must indicate a substantial improvement in regional myocardial perfusion, which accords with the findings of other investigators.¹ Thus a total of 75 patients (87%) had a normal perfusion scintigram after coronary angioplasty. Despite the improvement in myocardial perfusion, radionuclide left ventriculography showed persistent exercise induced regional abnormalities of wall motion in 33% of patients investigated within six weeks and in 19% of patients at three to six months. The response of the ejection fraction to stress was abnormal in a similar proportion of patients. This discordance between the results of radionuclide perfusion imaging and left ventriculography was also noted by the investigators of the National Heart, Lung and Blood Institute.¹ Because radionuclide ventriculography has been shown by other investigators to be the more sensitive technique for the diagnosis of coronary artery disease^{4,5} the discordant findings in the present study are best explained by continuing subclinical myocardial ischaemia in the territory supplied by the dilated artery.

Not surprisingly the severity of the residual coronary stenosis after coronary angioplasty was a major determinant of continuing left ventricular dysfunction during follow up. Thus patients with a residual stenosis of $\leq 20\%$ (group 1) showed restoration of normal left ventricular function in most cases. Indeed, in only 14% of patients tested did ejection fraction fail to increase with stress. All the patients with a residual stenosis of 21 to 50% (group 2), on the other hand, continued to show left ventricular decompensation despite amelioration of symptoms. Clearly, therefore, in patients recovering from coronary angioplasty a residual stenosis of 21–50%, while fulfilling conventional criteria for angiographic success, does not ensure complete correction of the left ventricular response to exercise. Indeed early after angioplasty continuing left ventricular dysfunction may remain detectable by radionuclide ventriculography in patients with a residual stenosis of $< 20\%$. We identified nine patients of this type and all of them showed exercise induced reductions in left ventricular ejection fraction six weeks after angioplasty. Importantly, however, contractile function had recovered at six months in every case.

These observations indicate that after coronary angioplasty a residual stenosis of $< 50\%$ may continue to cause important (albeit subclinical) obstruction to coronary flow. This is in marked contrast with the usual experience in coronary artery disease when

stenoses of $< 50\%$ are usually of no functional significance.⁶ The explanation for this apparent paradox may lie in the mechanism of coronary angioplasty, which causes plaque rupture, intimal dissection, and adventitial stretching with or without local aneurysm formation.^{7,8} Thus despite dilatation of the diseased arterial segment the dynamics of coronary flow will remain significantly disturbed by the damage to the vessel wall. It is reasonable to assume, however, that healing and endothelialisation of the lesion will improve coronary flow, and this may account for the late recovery of left ventricular function seen in some group 1 patients with a residual stenosis of $< 20\%$.

Thus coronary angioplasty with a residual stenosis $\leq 20\%$ improves both myocardial perfusion and left ventricular function. Nevertheless, the improvement in left ventricular function may be delayed for up to three months until arterial healing at the angioplasty site is complete. When the residual stenosis is between 21 and 50% subclinical exercise induced left ventricular decompensation may persist.

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Electrophysiological study of young patients with exercise related paroxysms of palpitation: role of atropine and isoprenaline for initiation of supraventricular tachycardia

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SUMMARY Electrophysiological studies were performed in eight patients (four men and four women, mean (SD) age 24 (5) years with paroxysmal attacks of palpitation during or immediately after exercise. Five patients were competitive athletes at college. In two patients spontaneous supraventricular tachycardia during exercise was recorded by ambulatory electrocardiographic monitoring and in another it was induced by treadmill exercise testing. Two had dual atrioventricular nodal pathways, three had manifest atrioventricular accessory pathways, and three had concealed atrioventricular pathways. Programmed stimulation induced sustained supraventricular tachycardia in six patients—in two after intravenous injection of atropine sulphate (1 mg) and in four during infusion of isoprenaline (0.01 µg/kg/min). In one patient, non-sustained atrioventricular nodal reentrant tachycardia was induced during isoprenaline infusion. In the remaining patient, who had dual atrioventricular nodal pathways, tachycardia was not inducible. AH block prevented maintenance of reentry in five patients. In five patients shortening of the effective refractory period of the atrioventricular node with atropine (one patient) and isoprenaline (four patients) caused sustained supraventricular tachycardia.

The present study indicates that treatment with atropine and isoprenaline may be an important factor in the initiation of supraventricular tachycardia in patients with exercise related paroxysms of palpitation.

It is widely accepted that well trained athletes tend to have bradycardia.^{1,2} Nevertheless, there are rare reports of exercise related supraventricular tachycardia.³⁻⁵ Coelho *et al* reported various forms of tachycardia in young athletes, including five with paroxysmal supraventricular tachycardia.⁶ We report the electrophysiological findings in eight patients with exercise related paroxysmal palpitation.

Patients and methods

We studied eight patients (four men and four women,

mean (SD) age 24 (5) years) who were referred for electrophysiological study from October 1983 to September 1987 because of repeated paroxysms of palpitation during or immediately after physical exercise or both. Five of eight patients were competitive athletes at college. History taking, physical examination, 24 hour ambulatory electrocardiographic monitoring, and a symptom limited exercise test on a treadmill or ergometer were performed in all eight patients. We established that the paroxysms of palpitation were related to exercise, especially the intensity of exercise. The intensity of exercise was graded arbitrarily as follows: moderate = higher level of exercise than daily activity (for example warming up exercises); strenuous = actual training for competitive athletics (for example repeated trials of the 100 metre dash).

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ELECTROPHYSIOLOGICAL STUDY

Patients gave their informed consent to the electrophysiological study, which was performed while they were non-sedated and fasting. None of the patients had ever been treated with cardioactive drugs.

Three catheter electrodes (USCI 6F) were introduced percutaneously under fluoroscopic control into the femoral vein and positioned in the high right atrium, across the tricuspid valve for His bundle recording, and at the right ventricular apex. Left atrial potentials were recorded on an oesophageal lead (Medtronic 10F).⁹ Intracardiac potentials and the left atrial potential were filtered at 50–500 Hz and recorded simultaneously by leads I, aVF, and V1 on an ink jet recorder at paper speeds of 50–100 mm/s. Analogue data were also recorded on magnetic tape for later analysis.

A digital programmable stimulator (Fukuda Denshi, BC02) was used to give programmed stimulation with 2 ms rectangular pulses that were 1.5 times diastolic threshold. Programmed stimulation was performed as follows: (a) extrastimulation (S2) was delivered from the high right atrium with a 10 ms reduction in the interval between stimuli every six sinus or atrial paced (S1) beats (the basic paced cycle lengths ranged from 750 to 400 ms); (b) incremental atrial pacing up to 200 beats/min; (c) extrastimulation (S2) delivered from the right ventricular apex after every six ventricular paced (S1) beats; and (d) incremental right ventricular stimulation up to 200 beats/min. Because basic programmed stimulation did not induce supraventricular tachycardia in any of the eight patients, 1 mg of atropine sulphate was injected intravenously and the study was repeated five minutes later. If induction of tachycardia did not follow injection of atropine, isoprenaline was infused at a rate of 0.01 µg/kg/min. The study was repeated five minutes after the start of isoprenaline infusion. Each episode of induced

tachycardia was terminated by either rapid atrial pacing or extrastimulation.

The following definitions¹⁰ were used:

- (a) A1 and V1 are the atrial and ventricular electrograms of the sinus or basic drive beat; and A2 and V2, the atrial and ventricular electrograms of the extra-stimulus.
- (b) The effective refractory period of the atrium is the longest S1S2 interval that failed to result in atrial depolarisation.
- (c) Effective refractory period of the atrioventricular node: the longest A1A2 interval in the His bundle electrogram that failed to propagate to the His bundle.
- (d) The effective refractory period of the accessory pathway was deemed to be the longest A1A2 interval that failed to propagate to the ventricle via the accessory pathway (anterograde) and the longest V1V2 interval that failed to propagate to the atrium via the accessory pathway (retrograde).

The diagnosis of atrioventricular nodal reentrant tachycardia and orthodromic atrioventricular reentrant tachycardia was based on established criteria.^{11,12} Premature atrial capture by ventricular extrastimulation and/or eccentric atrial activation during tachycardia were mandatory for diagnosis of atrioventricular reentrant tachycardia. A tachycardia was considered to be sustained if it lasted at least one minute and required stimulation for its termination. Tachycardia that lasted one minute or less was described as "non-sustained".

Results

Table 1 gives the clinical data. Patient 7 had pure posterior myocardial infarction possibly caused by Kawasaki's disease. Infarction was diagnosed by coronary angiography but the patient was symptom free during exercise except for paroxysms of palpita-

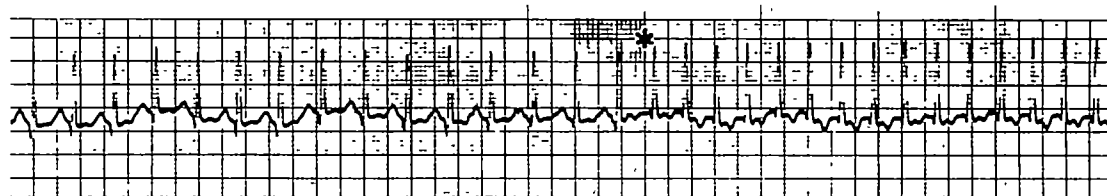
Table 1 Data on the patients and the results of electrophysiological study

Case No	Age (yr) and sex	History of palpitation*	PSVT		Induction of PSVT by programmed stimulation			Basis	Mechanism
			Exercise test	24 hour ECG monitoring	Control	Atropine	Isoprenaline		
1	20 F	1	—	—	Ac	+	—	WPW	AVRT
2	20 F	1	—	—	—	+	—	C-WPW	AVRT
3	24 M	2	—	+	Ac	±	+	C-WPW	AVRT
4	34 F	2	—	+	—	±	+	WPW	AVRT
5	23 M	2	—	—	Ac	Ac	+	WPW	AVRT
6	19 M	2	—	—	Ac	Ac	+	C-WPW	AVRT
7	33 M	2	+	—	—	—	±	DAVN	AVNRT
8	23 F	2	—	—	—	—	—	DAVN	—

*Palpitation occurred during moderate exercise (1), and strenuous exercise (2). See text for details.

Ac, single atrial echo; AVRT, atrioventricular reentrant tachycardia; AVNRT, atrioventricular nodal reentrant tachycardia; DAVN, dual atrioventricular nodal pathways; ECG, electrocardiography; PSVT, paroxysmal supraventricular tachycardia; WPW, Wolff-Parkinson-White syndrome; C-WPW, concealed WPW; +, sustained PSVT; ±, non-sustained PSVT; —, no PSVT.

Start of PSVT



End of PSVT

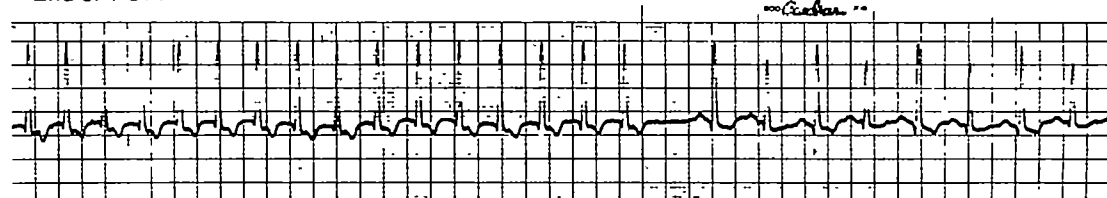


Fig 1 Spontaneous paroxysmal supraventricular tachycardia (PSVT) was recorded by 24 hour electrocardiographic monitoring (CMS lead) in patient 4 while she was skiing. The asterisk indicates the start of paroxysmal supraventricular tachycardia. The heart rate was slowed by an atrioventricular block before the end of tachycardia. Strips are not continuous.

tion. Patients 1 and 2 had had episodes during moderate exercise, and the remaining six patients (3 to 8) had episodes only during and/or immediately after strenuous exercise. Spontaneous paroxysmal supraventricular tachycardia was documented during an exercise test in one patient, and by 24 hour electrocardiographic monitoring in another two patients while they were exercising (fig 1, table 1). In these patients supraventricular tachycardia stopped spontaneously when exercise ended.

ELECTROPHYSIOLOGICAL STUDY

Atropine was given to all eight patients and isoprenaline to six patients. Table 2 shows the changes in effective refractory periods of the right atrium, atrioventricular node, and accessory pathway. There

were dual atrioventricular nodal pathways in two patients (cases 7 and 8), a manifest accessory pathway in three (cases 1, 4, and 5), and a concealed accessory pathway in three (cases 2, 3, and 6). Because of atrioventricular nodal Wenckebach periodicity in the control state and shortening of sinus cycle length after injection of atropine or during isoprenaline infusion, the effective refractory periods and induction of tachycardia were measured at different basic cycle lengths in six of the eight patients (table 2). Atropine shortened effective refractory periods of the atrioventricular node in all eight patients, although in five of these the basic cycle lengths shortened after atropine injection (see Discussion). Changes in the effective refractory period of the accessory pathway after atropine injection could be determined at the

Table 2 Electrophysiological data (ms)

Case No	Control					Atropine					Isoprenaline				
	ERP					ERP					ERP				
	BCL	RA	AVN	a-AP	r-AP	BCL	RA	AVN	a-AP	r-AP	BCL	RA	AVN	a-AP	r-AP
1	600	320	380	450	300	600	210	300	420	<270	*	*	*	*	*
2	750	230	500	—	<280	500	200	310	—	<250	*	*	*	*	*
3	500	*	W	—	*	500	200	310	—	<250	*	*	*	*	*
	750	300	360	—	300										
	600	*	W	—	*	600	230	280	—	280	500	240	250	—	*
4	500	250	>330	330	320	500	170	260	320	310	400	<250	<250	270	*
5	1000†	280	<340	400	*	750†	240	<320	390	*	450†	230	<270	280	*
6	600	300	370	—	320	600	260	310	—	310	600	270	<270	—	300
7	750	250	510	—	—	750	250	300	—	—					
						500	*	W	—	—	500	<200	<250	—	—
8	1000	290	490	—	—										
	600	*	W	—	—	600	210	380	—	—	400	200	210	—	—

*Not determined. †Sinus cycle length. In patient 5 the interval between the atrial electrogram and stimulus artefact on high right atrial electrogram was expressed as the effective refractory period of the right atrium.

AVN, atrioventricular node; a-AP and r-AP, anterograde and retrograde conduction of accessory pathway respectively; BCL, basic paced cycle length; ERP, effective refractory period; RA, right atrium; W, Wenckebach phenomenon.

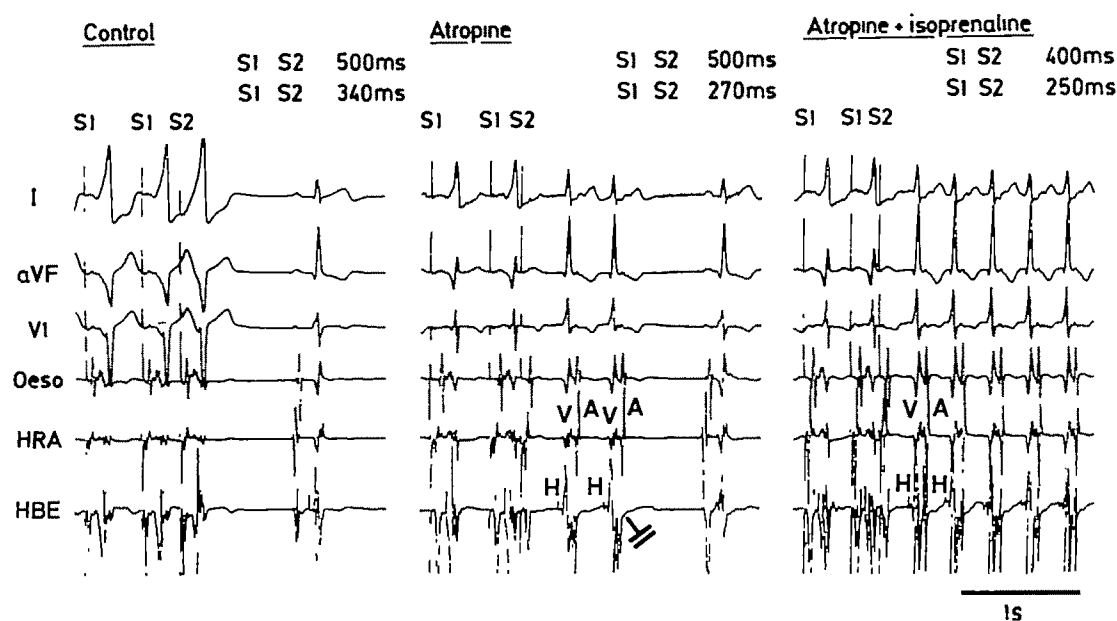


Fig 2 Electrophysiological study of patient 4 by electrocardiographic leads I, aVF, and V1; oesophageal lead (Oeso); high right atrial electrogram (HRA); and His bundle electrogram (HBE). During infusion of isoprenaline the spontaneous sinus cycle length shortened to 400 ms. In the control state, premature atrial stimulation (S2) at a coupling interval (S1S2) of 340 ms did not induce a reciprocating beat, and S2 at an S1S2 interval of 330 ms failed to result in atrial depolarisation. After atropine injection S2 provoked two reciprocating beats, but atriohisian block prevented continuous reciprocation. During isoprenaline infusion, atrioventricular reentrant tachycardia was induced by an S1S2 interval of 250 ms. During tachycardia the oesophageal lead of the left atrial electrogram coincided with the lower atrial electrogram from the His bundle. Diagnosis of atrioventricular reentrant tachycardia was based on premature atrial capture by ventricular stimulation when the His bundle was refractory. A, atrial electrogram, H, His bundle potential, V, ventricular electrogram.

basic cycle length identical to control in only two patients (1 and 4). Isoprenaline shortened the sinus cycle from 1033 (140) ms to 523 (81) ms ($p < 0.01$). The effective refractory period of the atrioventricular node was shortened further by isoprenaline infusion in five patients, although basic pacing cycle lengths were shortened during infusion (see Discussion). Isoprenaline-induced changes in the effective refractory period of accessory pathway were determined at the basic cycle length identical to that during the control state in patient 6 only. Figure 2 shows a representative example of induction of supraventricular tachycardia by programmed stimulation in patient 4 whose spontaneous supraventricular tachycardia is shown in fig 1. In the control state, supraventricular tachycardia was not induced in any patient. In four patients, single atrial echo which did not propagate to the ventricle because of atriohisian block was induced with programmed stimulation.

When the eight patients were given intravenous atropine injection, sustained supraventricular tachycardia was induced in two and non-sustained

supraventricular tachycardia in another two (table 1). In the two patients (cases 5 and 6), single atrial echo was also induced but did not propagate to the ventricle after atropine injection. Isoprenaline was then infused in six patients in whom sustained supraventricular tachycardia was not induced after atropine injection. During isoprenaline infusion, sustained supraventricular tachycardia was induced in four patients and non-sustained supraventricular tachycardia in one patient. Supraventricular tachycardia was not sustained because of an atriohisian block after atropine injection in two patients and during isoprenaline infusion in one patient. In patient 8, tachycardia was not induced even during isoprenaline infusion. In summary, sustained reentry was facilitated by shortening of the effective refractory period of the atrioventricular node by atropine in one patient (case 1) and by isoprenaline in four (cases 3, 4, 5, and 6).

TREATMENT

Patient 7 was advised against strenuous exercise and treated with oral verapamil (120 mg daily). The

remaining seven patients were allowed to continue their athletic activities because their paroxysms of palpitation subsided as soon as exercise stopped.

Discussion

We found that atropine or isoprenaline was required to shorten the effective refractory period of the atrioventricular node for supraventricular tachycardia to be sustained in five of eight patients with paroxysms of palpitation related to exercise. Isoprenaline infusion was necessary to induce supraventricular tachycardia in those who had had episodes of palpitation during strenuous exercise. The basis for the arrhythmia included dual atrioventricular nodal pathways in two and manifest or concealed atrioventricular bypass in six of the eight patients.

ELECTROPHYSIOLOGICAL STUDIES OF EXERCISE RELATED SUPRAVENTRICULAR TACHYCARDIA

Supraventricular tachycardia is induced during exercise in from 0.1 to 2.8% of the population and it is less common than exercise related ventricular tachycardia or premature ventricular complexes.³⁻⁵ Electrophysiological data on cases of exercise related supraventricular tachycardia are limited.^{6,8} Coelho *et al* reported that four of five cases of exercise related supraventricular tachycardia had an atrioventricular accessory pathway and atrioventricular reentrant tachycardia.⁶ Shortening of the atrioventricular nodal refractory period by isoprenaline and atropine was necessary to sustain supraventricular tachycardia in one and two cases respectively.⁶ In two of five patients in Coelho *et al*'s study supraventricular tachycardia occurred only during treadmill exercise at a high level.⁶

Akhtar *et al* reported on five cases of atrioventricular nodal reentrant tachycardia induced only by programmed stimulation after atropine injection.¹³ In three of five cases, the anterograde limb of the atrioventricular nodal reentrant pathway was refractory to the reciprocating impulse in the control state and atropine was required to reduce the refractory period of the atrioventricular node sufficiently to permit continuous reciprocation. Hariman *et al* reported a case of catecholamine dependent atrioventricular nodal reentrant tachycardia in which isoprenaline infusion led to the induction of tachycardia by enhancement of ventriculoatrial conduction.¹⁴ Isoprenaline facilitated the initiation of atrioventricular reentrant tachycardia by Brugada *et al* in 21 patients including 14 patients with exercise related circus movement tachycardia.¹⁵ Induction was allowed mainly by facilitation of anterograde conduction via the atrioventricular node.¹⁵

Our results resemble those of Brugada *et al*¹⁵ and

also those of Coelho *et al*,⁶ although we found no ventricular tachycardia. Manifest and concealed atrioventricular accessory pathways were the common basis for arrhythmia in the present study as in that of Coelho *et al*.⁶ Because vagal activity is increased in athletes the effective refractory period of the atrioventricular node had to be shortened with atropine (one patient) or isoprenaline (four patients) in order to sustain supraventricular tachycardia in our study. Shortening of the basic cycle length may have been an additional mechanism facilitating the induction of sustained supraventricular tachycardia after atropine (one patient) and induction of non-sustained supraventricular tachycardia during infusion of isoprenaline (one patient).

LIMITATIONS

The present study has several limitations. Firstly, only three of eight patients showed spontaneous arrhythmia. Therefore, the induced supraventricular tachycardia might not have been the cause of exercise related paroxysms of palpitation in the remaining five patients; none the less, four of them said that the palpitation that they experienced during induced tachycardia was similar to their exercise related palpitation. Secondly, comparison of effective refractory periods of the right atrium, atrioventricular node, and accessory pathway after drug injection was hampered by the different basic cycle lengths used. Additionally, the presence of an accessory pathway prevented precise determination of the effective refractory period of the atrioventricular node. Injection of atropine or isoprenaline, however, facilitated conduction via the atrioventricular node. The refractory period of the atrioventricular node is known to lengthen as the basic cycle length gets shorter.¹⁶ A decrease of basic cycle length per se could shorten the right atrial effective refractory period¹⁶ and might facilitate induction of supraventricular tachycardia by programmed stimulation. However, shortening of the effective refractory period of the atrioventricular node with atropine or isoprenaline provided an important basis for continued reciprocation. Thirdly, a treadmill or ergometer exercise test provoked supraventricular tachycardia in only one patient. This low rate of provocation of tachycardia with an exercise test might be because exercise was not as strenuous as that reported by Coelho *et al*.⁶ Finally, the mechanism of palpitation in patient 8 remained uncertain. We should have tested a higher dose of isoprenaline infusion.

CLINICAL IMPLICATIONS

The present data and the results of Coelho *et al*⁶ show that an exercise test rarely induces supraventricular tachycardia in patients with exercise related

supraventricular tachycardia. Atropine and isoprenaline are needed to induce supraventricular tachycardia in those who under control conditions do not show this arrhythmia. We found that injections of atropine or isoprenaline were needed before supraventricular tachycardia could be induced by programmed stimulation in athletes with enhanced vagal activity.

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Electrocardiographic findings and frequency of arrhythmias in Bartter's syndrome

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SUMMARY Twenty four hour electrocardiograms in 20 patients with Bartter's syndrome, a disorder associated with chronic potassium deficiency, were analysed for atrial and ventricular extrasystoles, pauses (RR interval > 2 s), and heart rate. The 12 lead resting electrocardiogram was also evaluated. There were slight electrocardiographic changes with ST segment depression (≥ -0.5 mm) in seven patients, flat or low amplitude T waves in seven, and U waves ($\geq +1.0$ mm) in three patients. The QT interval was prolonged in 18 patients. Nine patients had one or more ventricular extrasystoles in 24 hours. Only two patients had more than 200 ventricular extrasystoles in 24 hours. No patient had ventricular tachycardia. A total of nine patients had one or more atrial extrasystoles in 24 hours, but only one patient had more than 200 in 24 hours. One patient had an attack of non-sustained supraventricular tachycardia. No patient had pauses.

Dangerous tachycardia was rare in these patients with chronic potassium deficiency caused by Bartter's syndrome. The general pattern of slight electrocardiographic changes may reflect an adaptation of the myocardium to hypokalaemia. Further studies are, however, needed to determine whether these findings are relevant to long term prognosis.

Potassium is responsible for most electrolyte induced disturbances of cardiac rhythm. Although several studies have shown an increase in potentially dangerous ventricular arrhythmias in patients with hypokalaemia,¹⁻³ the subject is still highly controversial.^{4,5} The cause and effect relation is obscured by inadequate study techniques and by the tendency for arrhythmia associated with the underlying diseases.

Studies with microelectrodes in rabbits showed that alterations in potassium concentrations may cause significant changes in depolarisation, repolarisation, and pacemaker activity in various cardiac cells.^{6,7} A decrease in extracellular potassium concentrations results in a more negative resting membrane potential,⁸⁻¹⁰ a prolonged action potential duration,^{8,11} and an increased slope of spontaneous diastolic depolarisation.¹¹ Theoretically, these changes could lead to increased automaticity,¹¹ slowed conduction,⁹ and/or increased dispersion of repolar-

isation and refractoriness,¹¹ which may lead to tachycardia as well as to various types of conduction disturbances.¹²⁻¹⁴ There are not many studies of the electrophysiological effects of magnesium and its interaction with potassium.¹⁵

Several studies reported a correlation between the surface electrocardiogram and changes in the action potential resulting from alterations in potassium concentrations.^{6,9} Although the surface electrocardiogram does not give precise information on the electrical behaviour of the cell, it represents the sum of all depolarisation and repolarisation of the myocardial fibres and has therefore been used to assess disturbances in electrolyte balance.

Bartter's syndrome is characterised by renal potassium wasting, hypokalaemic alkalosis, hyperreninaemia, and normal blood pressure.^{16,17} Hypomagnesaemia is also common.¹⁸ The primary defect is thought to be a renal tubular dysfunction. Bartter's syndrome is a rare hereditary disorder that is often recognised by the incidental finding of chronic hypokalaemia in an otherwise apparently healthy individual.¹⁸ The clinical significance of this chronic electrolyte disturbance is unknown. We have assessed the prevalence of atrial and ventricular

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arrhythmias and have critically evaluated the electrocardiographic changes in these patients.

Patients and methods

PATIENTS

We studied 20 patients (seven men and 13 women) in whom Bartter's syndrome was diagnosed from 1972 to 1988. The mean age at the time of the study was 44.3 years (range 24 to 69 years). All patients showed renal potassium wasting with hypokalaemia, hyperreninaemia, high or high normal urinary aldosterone excretion, and they were all normotensive. Other causes of potassium wasting—that is, renal tubular acidosis, vomiting, or abuse of diuretics—had been excluded. The plasma concentration of bicarbonate was raised or high normal, urinary chloride excretion was normal, and repeated screening for diuretics in urine was negative in all patients. No patient was taking cardioactive drugs. The long term follow up of 19 of these 20 patients has been reported elsewhere.¹⁶ Eleven patients have also been examined by bicycle ergometer stress testing and cross sectional echocardiography. Of the eleven patients who underwent an exercise test, all except one reached the predicted maximal workload and pulse rate (unpublished observations). Table 1 summarises the clinical details.

METHODS

All patients had a physical examination, a 12 lead resting electrocardiogram, and 24 hour ambulatory

Holter monitoring. Blood samples for the analysis of serum potassium, magnesium, and calcium were obtained at the time of the studies.

Electrocardiogram

The electrocardiograms were recorded on paper at a paper speed of 50 mm/s on a six channel Mingograph (Siemens Elema 82) for the analysis of PQ intervals, QRST intervals, deviations in ST segments, and amplitude of QRS complexes, T waves, and U waves. One mV corresponded to 10 mm. All measurements were made in leads II and V4. Each electrocardiogram was also interpreted according to the Minnesota code.¹⁹ The QT interval was defined as the time from QRS onset to (a) the end of the T wave (QTE) and (b) the point at which the tangent of the T wave descent crossed the baseline (QTtan).²⁰ When the end of the T wave was obscured by an U wave, the T wave offset was taken as the time of intersection of the T and U wave.²¹ QT measurements were corrected for heart rate (QTc) by Bazett's formula.²² The upper limit of normal of QTc was defined as 0.425 s for men and 0.44 s for women.²² The mean value of three consecutive measurements was used in the analysis.

The electrocardiographic patterns were classified as showing changes that were "typical" of or "compatible" with hypokalaemia or "no significant changes", as described by Surawicz *et al.*²³ Classification was based on: (a) ST segment depressions ≥ 0.5 mm, (b) U wave amplitude $> +1$ mm, and (c) U wave amplitude larger than T wave amplitude in the

Table 1 Clinical and laboratory data and electrocardiographic measurements in 20 patients with Bartter's syndrome

Case No	Age (yr) and sex	Serum		PQ	QRS	QTE*		QTtan*		ST		T wave		U wave	
		K (mmol/l)	Mg (mmol/l)			II	V4	II	V4	II	V4	II	V4	II	V4
1	46 F	2.8	0.5	0.18	0.11	0.46	0.42	0.44	0.41	-0.5	0	3.0	2.3	0.4	0.4
2	38 F	2.3	0.5	0.15	0.09	0.45	0.45	0.46	0.43	-0.7	-0.5	2.2	2.7	0.7	0.7
3	59 F	2.4	0.5	0.18	0.07	0.45	0.45	0.45	0.48	0	0	1.2	0.8	0.3	0.3
4	27 F	3.0	0.8	0.14	0.08	0.40	0.41	0.39	0.41	0	0.5	3.7	3.2	0.7	0.7
5	44 F	2.4	0.6	0.14	0.10	0.48	0.47	0.47	0.46	-0.3	-0.4	2.5	2.8	0.6	0.7
6	38 F	2.9	0.7	0.14	0.09	0.45	0.44	0.43	0.43	-0.5	-0.4	3.0	2.5	0.5	0.4
7	24 F	2.9	0.5	0.15	0.10	0.42	0.43	0.40	0.41	0	0.5	3.5	4.8	0.1	0.2
8	66 F	2.8	0.4	0.15	0.08	—	0.49	—	0.53	-1.0	-0.5	1.0	1.3	—	—
9	43 F	3.1	0.6	0.11	0.09	0.47	0.48	0.47	0.47	-0.3	-0.2	1.5	1.5	0.4	0.3
10	40 F	3.3	0.8	0.19	0.08	0.46	0.47	0.46	0.45	0	0	2.0	2.0	0.7	0.4
11	43 F	2.3	0.7	0.17	0.12	0.49	0.48	0.46	0.44	0	0.5	4.0	4.2	0.8	0.3
12	34 F	3.0	0.7	0.15	0.11	0.47	0.47	—	—	0	0	0	—	0.3	0.5
13	34 F	2.9	0.5	0.14	0.10	0.47	0.46	0.45	0.44	-0.3	0	1.2	2.5	0.4	0.5
14	36 M	2.8	0.6	0.16	0.11	0.48	0.48	0.52	0.49	-0.5	-1.0	1.8	1.3	0.8	0.5
15	66 M	2.7	0.6	0.18	0.08	—	0.44	—	0.47	0	-0.5	0.5	0.5	0.5	0.5
16	45 M	2.4	0.6	0.16	0.10	0.42	0.41	0.45	0.43	0	0.5	2.5	3.0	1.2	1.1
17	35 M	2.7	0.6	0.19	0.09	0.62	0.62	0.52	0.53	0	0	4.5	8.0	—	—
18	54 M	2.8	0.5	0.19	0.09	0.45	0.51	0.49	0.48	0	0	3.0	4.8	1.1	1.2
19	28 M	2.4	0.5	0.14	0.09	0.45	0.43	0.48	0.42	0	0	2.0	3.3	1.0	0.8
20	69 M	2.5	0.6	0.16	0.10	0.45	0.46	0.46	0.46	0	-0.6	2.5	2.5	0.9	0.9

*Corrected for heart rate.

Normal limits of serum concentrations of potassium and magnesium at our laboratory are 3.6–4.5 mmol/l and 0.7–1.2 mmol/l respectively. Intervals are given in seconds. ST deviations and T and U wave amplitudes are given in millimetres. K, potassium; Mg, magnesium.

same lead. The electrocardiogram was classified as "typical" if three or more features were present in the two leads and as "compatible" if two features or one of the features related to the U wave were present.⁸

Holter monitoring

Ambulatory electrocardiographic recordings were obtained on two-channel 24 hour portable tape recorders (Reynolds Medilog) while the patients followed their daily activities. Each patient was asked to keep a diary of all activities during the recording. Tapes were analysed by a semiautomatic arrhythmia analyser (Reynolds Pathfinder)²⁴ operated by an experienced technician who was supervised by C B-L.

Ventricular extrasystoles were validated by the operator and analysed on printouts by C B-L. The number of false negative (missed) ventricular extrasystoles with this approach is negligible.²⁵ In three recordings with frequent ventricular extrasystoles (> 100 in 24 hours), the entire 24 hour electrocardiogram was printed out on paper and the beats counted manually. Premature normal events (that is those that occurred earlier than 30% of the preceding RR interval were defined as atrial extrasystoles) were detected on an uninterrupted replay.²⁴ This setting has been found empirically to give the best balance between the risk of missing atrial extrasystoles (false negatives) and noting false positives.²⁵ All premature normal events detected by the analyser were visually validated by the operator, who thereby minimised the number of false positive atrial extrasystoles. The electrocardiographic criteria for classification of extrasystoles were those of Friedman.²⁶ A pause was defined as an RR interval lasting > 2000 ms; compensatory pauses that followed premature QRS complexes were excluded.

We measured the mean 24 hour heart rate as the mean number of heart beats/min estimated from the total number of beats in 24 hours. The minimal heart rate was the smallest number of beats in one minute during a 24 hour period. When the normal limits for the mean 24 hour heart rate and for minimal heart rate were calculated we took into account the additive effects of age, sex, smoking, and physical activity.²⁷ The patient's participation in leisure time physical activity and their smoking habits were classified as described earlier.²⁷

STATISTICAL ANALYSIS

Values are expressed as mean (1 SD) unless otherwise stated. Pearson's coefficient of correlation was used to quantify the degree of relation between QT intervals in leads II and V4 and to assess the relation between electrocardiographic variables and serum concentrations of potassium and magnesium.

Results

No patient had a history of cardiovascular disease. Four patients reported infrequent palpitation. No patient had experienced faintness or syncope. One patient had chronic obstructive lung disease and diabetes mellitus (case 8). The physical examination was normal in all other patients.

ELECTROLYTES

The mean serum concentrations of potassium and magnesium were 2.7 (0.3) mmol/l and 0.6 (0.1) mmol/l respectively (table 1). Fifteen patients had hypomagnesaemia. The serum concentration of calcium was normal in every patient. There was no linear relation between the measured electrocardiographic variables and the serum concentrations of potassium or magnesium.

ELECTROCARDIOGRAPHIC FINDINGS

The PQ interval was normal in all patients and the mean value was 0.16 (0.02) s (table 1). Mean QRS interval was 0.09 (0.01) s; the interval was slightly prolonged in one patient (table 1).

Depression of the ST segment of ≥ 0.5 mm was found in seven patients, flat or low amplitude T waves in seven, and U wave amplitudes of ≥ 1 mm in three patients (table 1). The ST-T and U wave changes were generally slight (fig 1). By these electrocardiographic criteria seven patients had a pattern that was compatible with hypokalaemia (table 1). No patient showed a pattern that was typical of hypokalaemia on the resting electrocardiogram.

The QTc interval (onset of QRS to end of T wave) was measurable in both leads in all but two patients and the QTtan in all but three patients, in whom there was fusion with the U wave or the following P wave. All except two patients (cases 4 and 7) showed prolongation of the QTc and/or QTtan intervals (table 1). Figure 2 shows the group mean values of the QT intervals. Individual discrepancies of QT measurements between the two leads were related to the presence of superimposed U waves or delayed repolarisation changes.

HOLTER MONITORING

Nine (45%) patients had one or more ventricular extrasystoles in the 24 hour Holter recording (table 2). Two patients (cases 1 and 3) had more than 200 ventricular extrasystoles per 24 hour and one (case 7) had more than 1000. In both patients these were asymptomatic and multifocal with more than two QRS configurations, and in one of them they frequently occurred in pairs and in bigeminy. Of the remaining seven patients with ventricular extrasys-

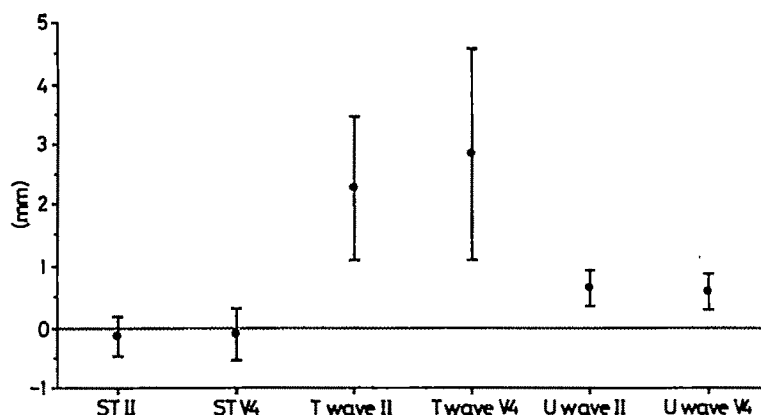


Fig 1 Mean (1 SD) ST segment deviations and T and U wave amplitudes in leads II and V4. Note the relation between the T wave amplitude and the U wave amplitude.

toles, one patient had two different QRS configurations, two had a single episode of R on T phenomenon, but none of them had pairs or episodes with bigeminy, trigeminy, or quadrigeminy. No patient had ventricular tachycardia.

Nine (45%) patients had one or more atrial extrasystoles in 24 hours, but only one patient (case 15) had more than 200 in 24 hours (table 2). One patient had a single episode of supraventricular tachycardia (case 20). The mean 24 hour heart rate was 79 (9) beats/min (range 62–90 beats/min). When corrected for age, sex, smoking habits, and physical activity the calculated mean 24 hour heart rate was higher than the predicted normal values in two patients (cases 15 and 18). In case 15 this may have been related to frequent atrial extrasystoles. The mean minimal heart rate was 56 (9) beats/min (range 41–70 beats/min). It was normal in all except two patients (cases 3 and 5), in whom it was lower than the predicted normal values. No patient had pauses (RR interval > 2.0 s).

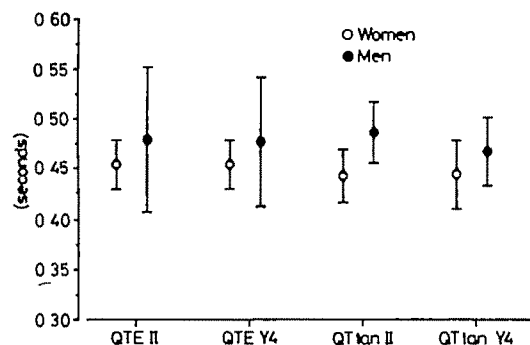


Fig 2 Mean (1 SD) QTE and QTan intervals in women and in men. The QT intervals are corrected for heart rate.

Discussion

Bartter's syndrome offers a unique opportunity to study clinical effects of chronic electrolyte disturbances. These patients have persistent, probably lifelong, hypokalaemia, often subnormal extracellular magnesium concentrations,¹⁸ and no apparent structural heart disease.

In most of our patients mean and minimal heart rates were normal after correction for smoking habits, age, and physical activity. In both experimental and clinical studies there is disagreement about the effect of low potassium concentration on the rate of the sinoatrial node^{9,28} but it is generally stated to depress the heart rate.²⁸

Only one patient had signs of conduction disturbances on the resting electrocardiogram or during 24 hour Holter monitoring. The PQ interval was normal in each patient and the QRS interval was also normal in all except one patient. Several experimental studies have documented a delay or block of atrioventricular conduction as the extracellular concentrations of potassium are lowered,^{9,29} and a diffuse depression of intraventricular conduction in more advanced hypokalaemia.⁹ In contrast with the high frequency

Table 2 Number of extrasystoles during 24 hour Holter monitoring in 20 patients with Bartter's syndrome

No of extrasystoles in 24 hours	VES No (%)	AES No (%)
None	11 (55)	11 (55)
>1	9 (45)	9 (45)
>10	5 (25)	3 (15)
>100	3 (15)	2 (10)
>200	2 (10)	1 (5)
>1000	1 (5)	0

VES, ventricular extrasystoles; AES, atrial extrasystoles.

of conduction defects in experimentally induced hypokalaemia, prolongation of the PQ or QRS intervals has been rarely seen in clinical hypokalaemia.³⁰

In clinical hypokalaemia the most consistent electrocardiographic changes are the appearance of a prominent U wave, depression of the ST segment, and decreased amplitude of the T wave.^{8,23,30} In our patients a pattern "typical" of hypokalaemia was not seen in any individual and a pattern "compatible" with hypokalaemia was seen in only a few. These patterns were more common in patients with other diseases who had comparable serum concentrations of potassium.^{8,23} Moreover, the magnitude of the ST segment depressions and the deviations in the amplitude of T and U waves were less pronounced in our patients.³⁰

In most of our patients the QT interval was prolonged. The relation of the QT interval to the serum concentration of potassium is controversial. Some have suggested that the QT interval is prolonged by hypokalaemia³⁰ and others that it is normal or actually shortened.^{21,23} Because there are several potential sources of inaccuracy in measuring the QT intervals in the clinical setting^{31,32} it is difficult to evaluate the biological significance of minor QT changes and to use the QT interval as a reliable reflection of repolarisation changes.³³ It is, however, well known that a decrease in extracellular potassium concentrations affects repolarisation by prolonging the action potential duration.^{6,8,11}

The slight general electrocardiographic changes in our patients contrasted with those in previous studies.^{23,30} Although changes on the electrocardiogram have usually been related to abnormalities in the extracellular electrolyte concentrations, it is the altered potassium gradient across the cell membrane that induces changes on the electrocardiogram.⁸ In acute experiments, intracellular potassium concentrations are relatively stable and altered potassium gradients are largely caused by the changes in extracellular concentrations of potassium. In our patients, however, the intramyocardial potassium concentration, and thus also the gradient across the myocardial cell membrane, is unknown. There are, however, a multitude of factors (see below) that make it difficult to compare electrocardiographic and electrophysiological changes in various states of hypokalaemia.

Supraventricular and ventricular tachycardia seemed to be no more common than in healthy subjects.^{23,34} All except two of our patients had a normal 24 hour Holter recording according to the recently suggested normal limit for the number of atrial and ventricular extrasystoles in 24 hours,²⁵ that is 200 extrasystoles in 24 hours. The significance of

the single episodes of R on T phenomenon seen in two other patients with less than 200 ventricular extrasystoles in 24 hours was hard to evaluate because most of the complex extrasystoles can occur as incidental findings in a few healthy subjects.^{25,34} In previous studies patients with hypokalaemia had more extrasystoles than a control hospital population.^{1,30} Studies with microelectrodes in rabbits showed that continued perfusion with solutions containing low concentrations of potassium leads to supraventricular and ventricular extrasystoles, ectopic tachycardia and, finally, ventricular fibrillation.⁹ The tendency for extrasystoles to develop during hypokalaemia has been attributed to several electrophysiological effects, including an enhanced automaticity, a prolonged phase 3 of the action potential duration, and an enhanced reentry caused by depressed conduction.¹²

The type of rhythm disorder induced or abolished by changes in the serum concentration of potassium depends not only on the extracellular potassium concentration but also on other factors, such as the rapidity with which the potassium concentration changes, the sensitivity of the various cardiac fibres to such changes, the extracellular concentration of other electrolytes, the underlying state of the myocardium, the interactions with neurogenic factors, and cardioactive drugs.^{8,15} Moreover, studies in rabbits showed that cardiac muscle was protected against loss of potassium during chronic potassium depletion by an adaptive increase in the density of sodium pump receptors.³⁵ It is not yet known whether these results can be extrapolated to human beings.

We found that although extracellular concentrations of potassium were usually very low in patients with Bartter's syndrome, the electrocardiographic changes were slight and arrhythmias were not common. Further studies will be needed to show whether these findings are relevant to the long term prognosis.

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Sinus arrhythmia in children with atrial septal defect: an analysis of heart rate variability before and after surgical repair

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SUMMARY The expression of sinus arrhythmia depends on separation of the systemic and pulmonary venous return to the heart as well as on normal autonomic control mechanisms. Patients with atrial septal defect provide a naturally occurring experiment of communication between the two venous systems. In adults with atrial septal defect sinus arrhythmia is minimal or absent. But children with atrial septal defect retain appreciable sinus arrhythmia, although this is not recognised in published reports. To understand why this is so, continuous electrocardiograms were recorded before and after operation in 10 children (aged 4-16 years, mean 6.3) with atrial septal defects and in 10 normal children (aged 5-7 years, mean 6.1). Mean RR intervals were calculated for periods of one minute, and the standard deviation was used as an index of heart rate variability (that is sinus arrhythmia). Frequency analysis (spectral analysis) was also performed on a continuous beat to beat record of heart rate to describe the frequency components that may reflect autonomic activity. The results confirmed the presence of considerable sinus arrhythmia in children with unoperated atrial septal defect. None the less, the standard deviation of RR intervals in the children with unoperated atrial septal defect was significantly less than that for the normal children, and variation increased after closure of the defect. Power spectral analysis of instantaneous heart rate indicated that the high frequency (0.15-0.45 Hz) vagally mediated component of variability was lower for patients than for controls which may indicate abnormalities of autonomic control of heart rate in these children. The comparative retention of sinus arrhythmia in children with atrial septal defect may relate to the small size of the right atrium or differences in myocardial compliance compared with adults.

Respiratory sinus arrhythmia is a normal feature of healthy individuals. Its presence depends on normal autonomic control of the heart and normal cardiac anatomy. Atrial septal defect is said to be characterised by decreased sinus arrhythmia or heart rate variability in adults¹ but this has not been proved in children. Our clinical observations (fig 1) did not suggest that a decrease in the variability of heart rate is characteristic of children with atrial septal defect.

This study was designed to compare heart rate variability in children with atrial septal defect before

and after operation, and to compare their variability with that of normal children. We also used frequency analysis (power spectral analysis) of the heart rate of these children to describe the frequency components in their heart rate variability that reflect autonomic activity and to examine the possible effects of closure of the atrial septal defect on autonomic regulation of the heart rate.

Patients and methods

We studied 20 children: 10 normal children aged five to seven (mean 6.1), and 10 aged four to 16 (mean 6.3) with atrial septal defect who were about to undergo operation. All patients with atrial septal defect were symptom free or had minimal symptoms, and clinical

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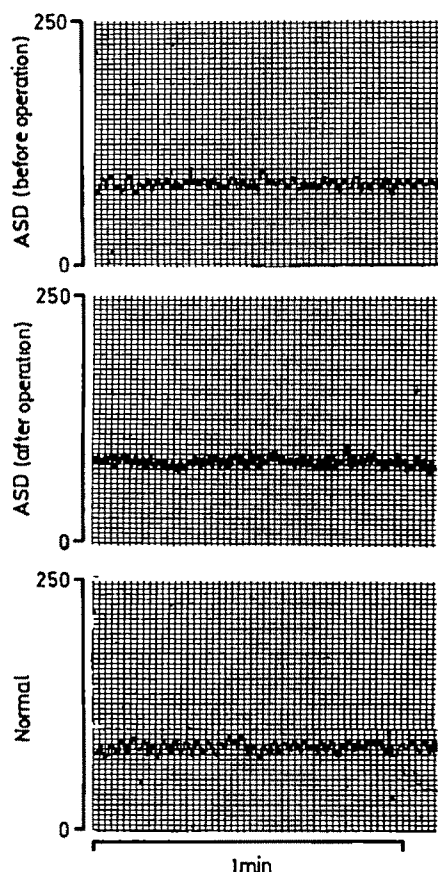


Fig 1 Instantaneous heart rate in a normal child and in a child before and after surgical closure of an atrial septal defect.

findings included a systolic murmur, a wide fixed split of the second heart sound, cardiomegaly on chest x ray, and right ventricular hypertrophy on electrocardiograph. Echocardiography confirmed the diagnosis of atrial septal defect in all. Cardiac catheterisation was performed in six patients and in these the pulmonary:systemic flow ratios ranged from 2.0 to 3.2 (mean 2.5). The defect was confirmed at operation in all cases: nine had isolated secundum atrial septal defect and one had a primum defect. The heart rate was recorded immediately before operation and 4.9 (2) months afterwards. All children had normal sinus rhythm.

We recorded heart rate and respiratory activity from electrocardiographic and impedance respiratory signals obtained from a Healthdyne apnoea-bradycardia monitor (model 16000-01). The electrocardiogram was converted to beat to beat heart rate by an analogue device² during simultaneous recording at a slow speed on paper and FM tape. A

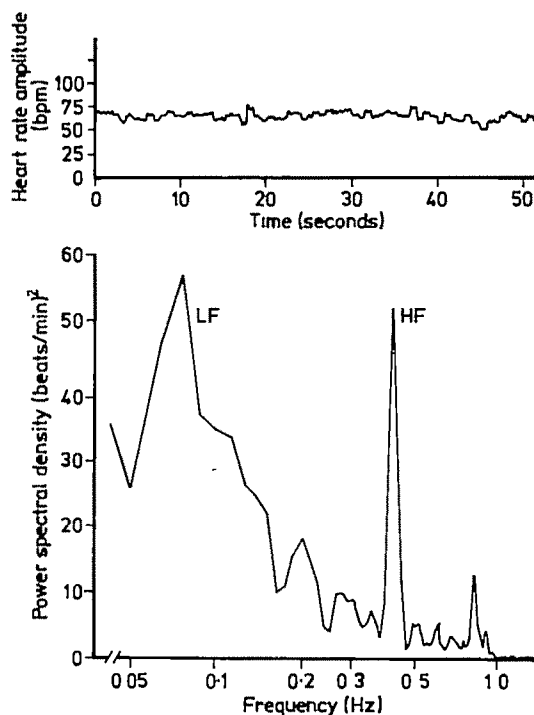


Fig 2 Instantaneous heart rate and corresponding power spectral density of subject showing prominent low frequency and high frequency peak.

brief initial period of familiarisation ensured that all the children were at ease with the apparatus. Children were asked to remain quiet but awake during the recordings, which lasted 10–15 minutes in total and were performed with the child standing and supine. We used both positions to evaluate two levels of autonomic tone: standing, high sympathetic and low parasympathetic; supine, low sympathetic and high parasympathetic tone.

We stored heart rate data for a one minute period for each position on a computer disc for subsequent analogue-digital conversion (rate 250 Hz) and processing. For computerised detection of the R wave we used the procedures of Wolf *et al*³ followed by human editing and data correction as described previously.⁴ The mean RR interval and standard deviation were computed for each posture for each patient.

In a separate analysis, a three to four minute segment of continuous stationary heart rate data for each position was processed by spectral analyser (Nicolet No 660A) according to previously published technique.² We selected a segment from the paper recording that was free of sudden changes in the respiratory activity such as sighs or movement

Table 1 Group mean (SEM) RR intervals and standard deviations of RR intervals (ms) for subjects in supine and upright positions

	No	RR	SD
Supine:			
Atrial septal defect (preop)	9	658 (184)	28.4 (21.3)
Atrial septal defect (postop)	10	739 (81)	48.7* (15.2)
Control	10	702 (96)	72.4* (36.8)
Upright:			
Atrial septal defect (preop)	9	591 (88)	31.4 (14.9)
Atrial septal defect (postop)	10	628 (54)	35.6 (12.3)
Control	10	610 (77)	47.2† (15.0)

* $p < 0.01$ v preop, † $p < 0.04$ v preop.

artefact. The power associated with the low frequency and high frequency peaks was determined as the square root of the area under each peak within 0.025 Hz of the low frequency peak and within 0.050 Hz of the high frequency peak (fig 2). Area ratios L:H were calculated.

Because the data were not normally distributed they were logarithmically transformed before being compared by two tailed t tests.

The research protocol was approved by the hospital ethics committee and informed consent was obtained from the children's parents.

Results

ANALYSIS OF THE RR INTERVAL

In both the supine and standing positions the mean RR intervals before operation and after operation in those with an atrial septal defect and in the controls were not statistically different (table 1). There was, however, a tendency for the RR interval to increase (decreased heart rate) after operation in the group with an atrial septal defect.

Heart rate variability in the supine position, as measured by the standard deviation of the RR interval, was significantly less before operation in those with atrial septal defects than in the controls (28.4 v 72.4 ms, $p < 0.01$), with very little overlap between the groups (fig 3). Also, the heart rate variability significantly increased after closure of the atrial septal defect (28.4 v 48.7 ms, $p < 0.01$). Although the results after operation overlapped with those of both the preoperative and control groups, the standard deviation of RR intervals increased after surgical repair in all but the oldest patient. The standard deviation after operation was not significantly different from that of the control group.

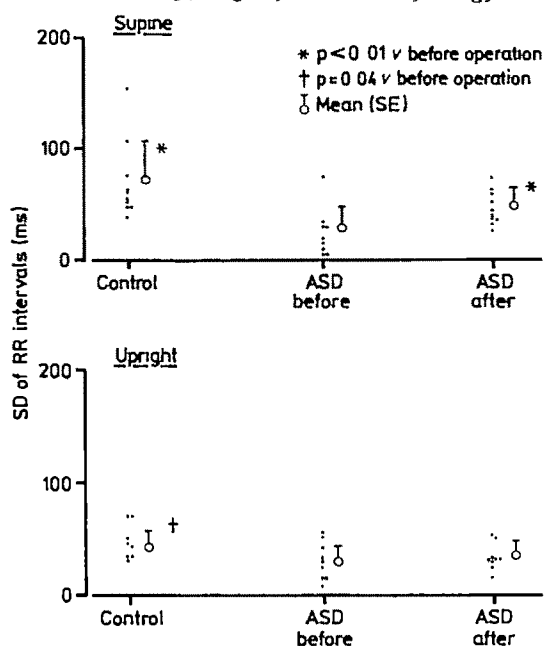


Fig 3 Standard deviation of RR intervals while individual is supine or upright of controls and of children before and after surgical closure of an atrial septal defect.

In the upright position the standard deviation of the RR intervals was also significantly lower before operation in those with an atrial septal defect than in controls (31.4 v 47.2 ms, $p < 0.05$), but it was not changed after surgical repair. There was no difference in respiratory rate between the three groups in either position.

SPECTRAL ANALYSIS OF BEAT-TO-BEAT HEART RATE

Heart rate variability was also assessed by spectral analysis. In both supine and upright positions there was considerable variation in the amplitude values (table 2, fig 4). In the supine position, those with atrial septal defects showed an increase of low frequency amplitude and of L:H after operation. These changes were not statistically significant, however. There was a decrease in high frequency amplitude which also did not reach significance. Control values were generally slightly higher than values before and after operation, significantly so in the case of high frequency ($p < 0.03$ v preoperative values, $p < 0.01$ v postoperative values). In all but one patient, values of L:H increased after operation. Individual low frequency and high frequency values showed no consistent response to operation. There was no correlation between changes seen in low frequency, high frequency, and L:H with operation.

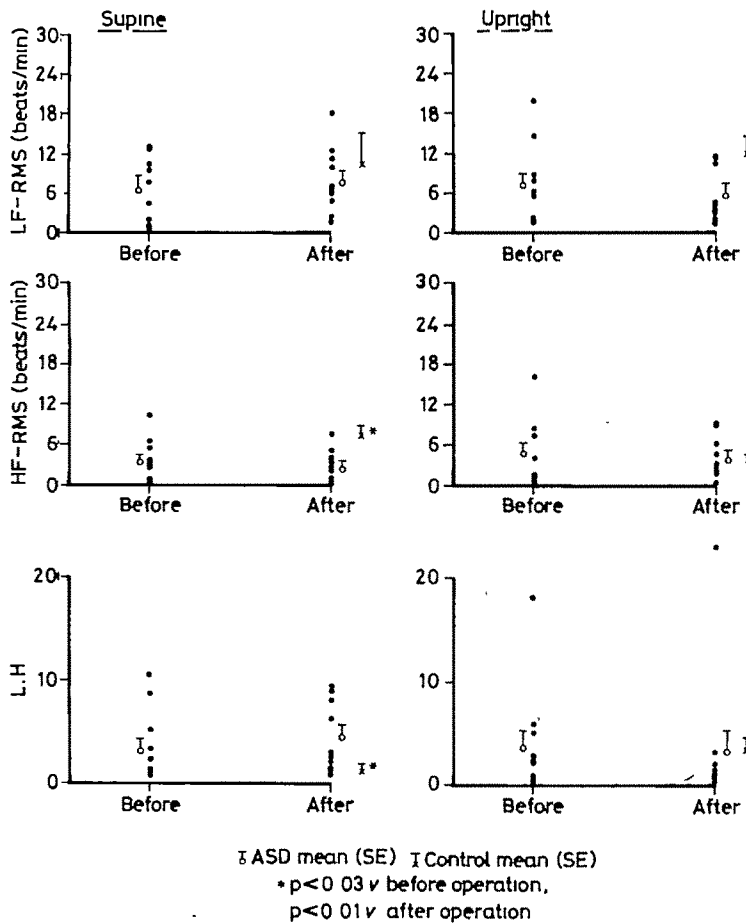


Fig 4 Low frequency and high frequency amplitudes and L:H ratio in supine and upright positions of patients before and after surgical closure of an atrial septal defect. Mean control values are also shown.

Table 2 Group mean (SEM) low frequency and high frequency spectral rms values (beats/min) and L:H ratio for subjects in supine and upright positions

	No	Low frequency	High frequency	L:H
Supine:				
Atrial septal defect (preop)	10	6.42	3.39	3.50
Atrial septal defect (postop)	10	1.58	1.04	1.04
Controls	10	8.10	2.88	4.34
		1.57	0.75	1.00
		4.86	1.44	0.45
Upright:				
Atrial septal defect (preop)	10	7.26	4.95	3.92
Atrial septal defect (postop)	9	1.90	1.63	1.70
Controls	10	5.91	4.43	3.64
		1.39	1.09	1.70
		12.0	4.01	3.69
		2.69	0.61	0.95

*p < 0.03 vs preop, p < 0.01 vs postop

In the upright position, there was a wider scatter of values with no consistent response with operation.

Discussion

This study confirms that although there is considerable variability in heart rate in children with atrial septal defect, it is less than that in normal children and that it increases after closure of the defect.

Heart rate variability is known to be greater in young children than in adults^{5,6}; this makes it more difficult to identify children with atrial septal defect. The substantial increase in heart rate variability in children with atrial septal defect compared with adults may be related to the smaller right atrium of children or to differences in ventricular compliance between adults and children.⁶

The fact that heart rate variability (measured by standard deviation of RR intervals) tends to become

normal after closure of the atrial septal defect suggests that it is dependent on the anatomical change within the heart. The two most important mechanisms producing sinus arrhythmia in normal persons are right atrial stretch with the inspiratory increase in systemic venous return and inspiratory inhibition of the carotid sinus reflex, both of which produce relative tachycardia.⁷ An atrial septal defect dampens the respiratory fluctuations of right atrial volume because there is communication between right and left atria⁸; further, with the larger right atrium of atrial septal defect, the inspiratory increase of right atrial volume is proportionately less than that occurring with a normal right atrium. This would contribute to diminished variability of the heart rate.

We used spectral analysis to study heart rate variability in these patients because of its potential to identify autonomic abnormalities of heart rate control that could also be responsible for decreased heart rate variability. Heart rate variability in people of all ages has two main frequencies of variation: a high frequency band, 0.15–0.45 Hz (3 second period) and low frequency band, 0.03–0.15 Hz (12 second period).^{6,10} The prominence of these two frequency bands in heart rate variability can be expressed by amplitude in the power spectrum. In general, the high frequency band corresponds to the respiratory frequency and is vagally mediated.^{10,11} The low frequency peak seems to be mediated by both the sympathetic and parasympathetic systems.^{10,11} A change in peak amplitude may be caused by changes in coupling between respiration and the heart or changes in autonomic control.

When the children were supine, both low and high frequency amplitudes were smaller in patients with atrial septal defect, both before and after operation, than in the controls, but there were no significant changes in amplitude with operation. Before operation RR interval standard deviations were low in accord with the lower preoperative spectral amplitudes in this group. Variability in the RR interval as seen in the standard deviations after operation was normal in contrast with the persistently low spectral amplitudes after operation. The low postoperative spectral amplitude may indicate residual autonomic abnormalities which later post-operative studies might clarify. In the present study, the considerable scatter of amplitude values within each of our groups permits only tentative conclusions.

Atrial septal defect in children is associated with

retention of considerable variability of the heart rate, although it is less than for normal children. Closure of the atrial septal defect is associated with an increase to normal variability. The possibility of abnormalities of autonomic control merits further study.

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Cross sectional echocardiography for recognition of ventricular topology in atrioventricular septal defect

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SUMMARY The cross sectional echocardiograms of 150 children with atrioventricular septal defects were reviewed to determine the spatial orientation of the ventricles. In 125 cases with usual atrial arrangement (situs solitus), ventricular topology showed the right hand pattern. Of the 25 patients with atrial isomerism, 13 had similar right hand topology but 12 (48%) had the left hand pattern. This finding was more common in hearts in the right side of the chest (dextrocardia), but there was no significant correlation between ventricular topology and number of atrioventricular valves or the ventriculoarterial connection. In part because of inferences for disposition of the conducting tissue, knowledge of ventricular topology is important when operation for atrioventricular septal defects is considered.

Ventricular topology can be promptly recognised by cross sectional echocardiography.

For hearts with both morphologically right and left ventricles, Van Praagh and his colleagues introduced the concept of right and left hand spatial orientation of the ventricles.¹ This concept is particularly important in describing hearts with an atrioventricular septal defect and atrial isomerism because the spatial orientation of the ventricles cannot be inferred from the category of atrioventricular connection.

Topology or topographical anatomy is the science of the description of a part of the body in terms of where it lies and its surrounding structures. In so-called right hand topology, it is the palmar surface of the observer's right hand that can be placed on the septal surface of the morphologically right ventricle, with the thumb in the tricuspid valve, the wrist in the apical trabecular component, and the fingers in the outlet. Such an arrangement is found in the normal heart. Left hand pattern topology, the mirror image arrangement, is characteristically found in hearts with congenitally corrected transposition with the usual atrial arrangement.

Patients and methods

One hundred and fifty consecutive cases of atrioventricular septal defects investigated echocardiographically between January 1983 and September

1986 were reviewed retrospectively. The atrial arrangement (situs) was inferred from analysis in short and long axis views of the abdominal great vessels. Cases with usual atrial arrangement (situs solitus) showed a left sided aorta and a right sided inferior vena cava at the level of the diaphragm. Atrial isomerism was inferred echocardiographically from the arrangement of the aorta and major venous structures in the abdomen. Left atrial isomerism was judged to be present when there was a venous structure posterior to the usually midline abdominal aorta. This posterior venous structure represented the azygous continuation of the inferior vena cava, and no normal inferior vena cava was seen. Right atrial isomerism was inferred when both the aorta and an anterior venous structure, shown to be the inferior vena cava in long axis view, were on the same side of the spine.²

Apical and subcostal four chamber sections were analysed to ascertain ventricular topology. Ventricles were identified as being of the right or left type on the basis of their anatomical features. In the morphologically right ventricle the atrioventricular valve shows chordal insertions into the ventricular septum (fig 1). The ventricle itself has an apical papillary muscle (fig 2), a septomarginal trabeculation (fig 3), and coarse trabeculations (fig 4). Conversely, the morphologically left ventricle was identified by absence of any chordal attachments to the septum (fig 1), the possession of characteristically paired papillary muscles, and a fine trabecular pattern (fig

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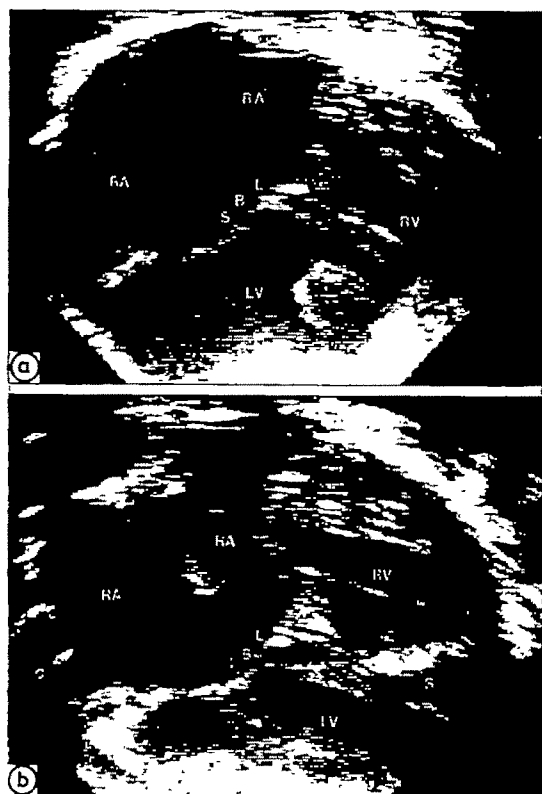


Fig 1 Atrioventricular septal defect with right atrial isomerism and left hand pattern topology. Note chordal insertions to the septum (S). RA, right atrium; RV, right ventricle; LV, left ventricle; SBL, superior bridging leaflet; IBL, inferior bridging leaflet.

4). In patients with atrial isomerism, we identified the cardiac position within the chest, the presence of a common or two separate atrioventricular valves, and the ventriculoarterial connections. These features of the heart were correlated with the ventricular topology.

Results

ATRIAL ARRANGEMENT

Among 150 patients with atrioventricular septal defects, 125 (83%) had lateralised atria, all with usual atrial arrangement. All were found to have right hand pattern ventricular topology (fig 4). The remaining 25 cases had atrial isomerism—13 had right and 12 left isomerism. In 13 (52%) of them topology showed a right hand pattern (fig 5) and in the other 12 patients it showed a left hand pattern (fig 1). Right and left hand patterns were similarly distributed in the two subgroups with atrial isomerism. Fifty four per cent of patients with right and 50% of those with

left isomerism showed topology with a right hand pattern.

CARDIAC POSITION

A left sided heart was present in 11 patients, 9 of whom had the right hand topological pattern. Eleven patients had a right sided heart and nine of these had a left hand pattern topology. The different associations are unlikely to be due to chance (χ^2 with Yates' correction, 6.5; $p < 0.05$). The remaining three patients had a heart in the middle of the chest, two of which had the right hand pattern.

MODE OF ATRIOVENTRICULAR CONNECTION

The atrioventricular junction had a common atrioventricular valve in 16 patients—10 with left and six with right hand pattern topology. Connection was through two separate atrioventricular valves in the

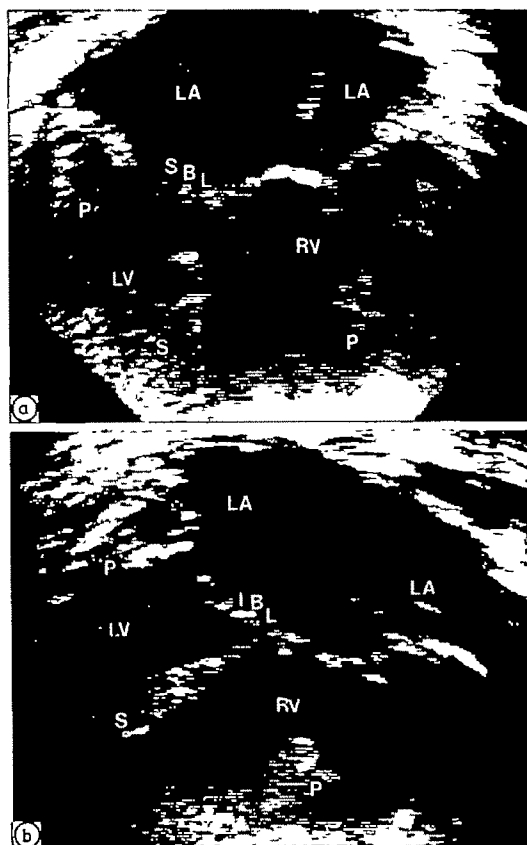


Fig 2 Atrioventricular septal defect with left atrial isomerism and left hand pattern topology. Note apical papillary muscle (P) of the right ventricle (RV). LA, left atrium; LV, left ventricle; S, interventricular septum; SBL, superior bridging leaflet; IBL, inferior bridging leaflet.

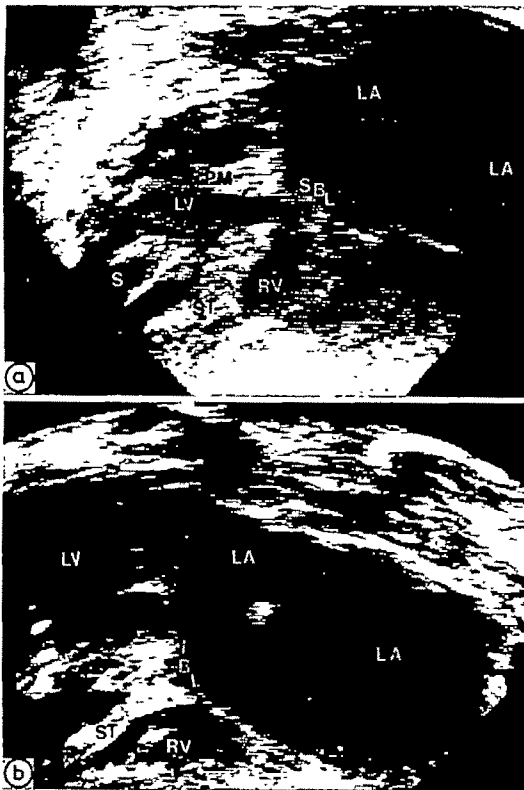


Fig 3 Atrioventricular septal defect with left atrial isomerism and left hand pattern topology. Note the septomarginal trabeculation (ST) of the right ventricle (RV) and the lateral papillary muscle (PM) of the left ventricle (LV). SBL, superior bridging leaflet; IBL, inferior bridging leaflet; S, interventricular septum; LA, left atrium.

remaining nine patients, seven of whom had a right hand topological pattern (fig 5). No significant difference was found between ventricular topology associated with the two modes of atrioventricular connections (χ^2 with Yates' correction, 2.30, NS).

VENTRICULOARTERIAL CONNECTIONS

The ventriculoarterial connections were predominantly concordant (11 cases) and double outlet right ventricle (11 cases). In the first group, the right hand pattern was identified in seven patients. This pattern was also found in five patients in the second group.

Discussion

In our series of patients with an atrioventricular septal defect, all hearts with the usual atrial arrangement had ventricular topology with a right hand pattern. That was not the case in the presence of atrial isomerism, when the left hand pattern was found in about half of the cases. This applied when

there were paired right atria or paired left atria. Thus while it is probable that atrial arrangement predicts ventricular topology when morphologically distinct left and right atria are present, atrial anatomy does not predict ventricular topology in the presence of atrial isomerism.

Right hand pattern topology was more common in left sided hearts as was the left hand pattern in right sided hearts. There is no significant correlation, however, between the mode of atrioventricular connection or ventriculoarterial connection and ventricular topology. Thus identification of ventricular morphology is the only reliable method to determine ventricular topology. Cross sectional echocardiography has proved to be a valuable and safe diagnostic tool in recognising the morphological features of each ventricle.

The concept of ventricular topology is important when surgical intervention is considered in patients with an atrioventricular septal defect because the distribution of the conduction system depends not only on the anatomical defect but also on topology. It is also well recognised that isomerism of the atrial

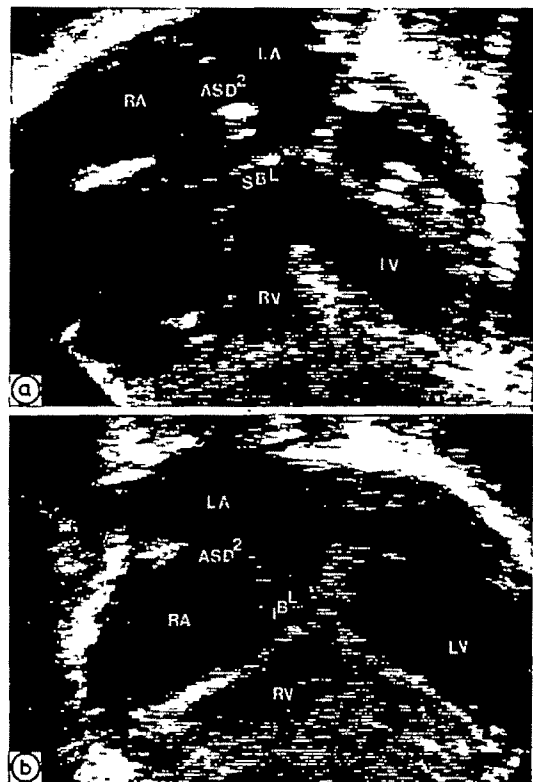


Fig 4 Atrioventricular septal defect with usual atrial arrangement and right hand pattern topology. Note also a secundum atrial septal defect (ASD²); RA, right atrium; LA, left atrium; RV, right ventricle; LV, left ventricle; SBL, superior bridging leaflet; IBL, inferior bridging leaflet.

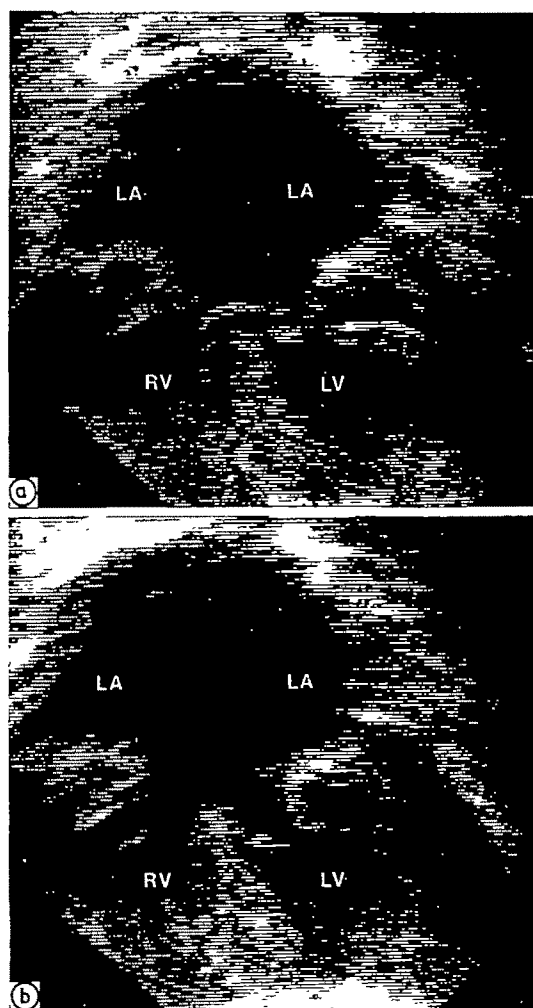


Fig 5 Atrioventricular septal defect with left isomerism and two separate atrioventricular valves with right hand pattern topology. LA, left atrium; RV, right ventricle; LV, left ventricle.

appendages disturbs the distribution of the conduction tissues. So the sinus node is abnormal irrespective of the other associated intracardiac abnormalities. There are two sinus nodes seen when there are bilateral right atrial appendages, whereas if both atrial appendages are of left morphology the sinus node, when present, will be hypoplastic and abnormally located in the lateral atrial wall, either on the right or left side.³ The arrangement of the atrioventricular junction is also abnormal.

In patients with atrioventricular septal defect and concordant connections (with usual or mirror image arrangement) the atrioventricular node is inferiorly displaced and lies in the posterior atrial wall beneath the orifice of the coronary sinus. The penetrating bundle is also displaced posteriorly and lies in the

posteroinferior rim of the ventricular component of the defect. The atrioventricular bundle then continues in an exposed position either along the crest or on the morphologically left ventricular aspect of the interventricular septum^{4,5} where it is at risk of trauma during surgical correction. With right hand topology therefore, sutures should be placed to the right side of the ventricular septum or to valve tissue on the right, whereas with left hand topology and mirror image arrangement sutures should be placed on the left side (morphologically right) of the septum.

When there is atrial isomerism and an atrioventricular septal defect the main determinant of the distribution of the ventricular conduction tissues is the spatial orientation of the ventricular mass. Right hand topology is always associated with a normal posterior atrioventricular node. With left hand pattern, paired atrioventricular nodes are usually present and there is a well defined sling of specialised conduction tissue between them. The sling, which may or may not connect the two atrioventricular nodes, runs on the inferior rim of the ventricular septal defect on the morphologically left side of the interventricular septum. The bundle branches arise from this sling. This again would be a reason for always placing sutures on the (morphologically) right ventricular aspect of the interventricular septum.

Dickinson *et al* reported a case of right atrial isomerism in which there was a second anterior atrioventricular node despite a right hand topological pattern.³ Thus while a regular conduction is to be expected when there is an ambiguous atrioventricular connection and right hand ventricular topology, and an anterior node and/or sling is usual with left hand topology, too few cases have been studied to establish anything more than guidelines. They do, none the less, confirm the crucial role of the concept of ventricular topology in these malformations.

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Cardiac abnormalities in the fragile X syndrome

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SUMMARY Twenty three patients with fragile X syndrome underwent cardiovascular assessment. Echocardiography showed dilatation of the aortic root in 12 (52%) and mitral valve prolapse in five (22%), four of whom had an apical mid-systolic click on auscultation.

Patients with fragile X syndrome have cardiac defects similar to those seen in other disorders of connective tissue such as Marfan's syndrome and Ehlers-Danlos syndrome. These, and other somatic features, suggest an underlying connective tissue dysplasia.

The fragile X syndrome is the commonest inherited cause of mental retardation and it affects approximately one in a 1000 males.^{1,2} It is so called because there is a fragile site on the long arm of the X chromosome in affected patients.³ Common somatic manifestations include a long face, large and prominent ears, prognathism, and macroorchidism. Other associated findings such as hyperextensible finger joints, pectus carinatum, a high-arched palate, and flat feet suggest an underlying connective tissue dysplasia.⁴ Previous reports of mitral valve prolapse and aortic root dilatation in patients with fragile X syndrome support this proposition.^{5,6}

This study was performed to establish the frequency of cardiac abnormalities in a population of patients with fragile X syndrome who underwent voluntary cardiac assessment.

Patients and methods

PATIENTS

We studied 23 men (aged 18-80, mean 51) with proven fragile X syndrome. Most were moderately or severely mentally handicapped. A few were living in the community while most were resident in a hospital for the mentally handicapped. They were drawn from a group of 28 patients identified by cytogenetic examination in a prospective survey of an inpatient population. Five patients did not consent to examination.

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METHODS

Each patient underwent clinical examination of the cardiovascular system. Special note was made of the clicks of mitral valve prolapse and murmurs of mitral and aortic valve regurgitation. All patients had a chest x ray, an electrocardiogram, and Doppler echocardiography. Cross sectional and M mode echocardiography were performed to look for mitral valve prolapse and aortic root dilatation; and continuous wave, pulsed wave, and colour Doppler were used to detect mitral and aortic regurgitation.

Mitral valve prolapse was diagnosed if there was systolic leaflet billowing into the left atrium in the parasternal long axis view and the point of coaptation of the mitral valve leaflets was displaced to above the atrioventricular ring.^{7,8} The aortic root dimensions were compared with the normal values based on age and body surface area reported by Feigenbaum.⁹

Results

CLINICAL EXAMINATION

Auscultation of the heart was normal in 17 patients. An isolated apical mid-systolic click was heard in two patients, and a classic mid-systolic click and late systolic murmur in two others, one of whom also had an early diastolic murmur in the aortic area. Two patients had an apical late systolic murmur without a click.

CHEST X RAY

Four patients had cardiomegaly (cardiothoracic ratio > 55%) but only one had clinical signs of mitral valve prolapse with mitral and aortic regurgitation. The chest x ray was normal in the remainder, although many patients showed poor inspiratory effort.

Table A comparison of fragile X, Marfan's, and Ehlers-Danlos syndromes and homocystinuria

Syndrome	Clinical manifestations	Mental retardation	Cardiac abnormalities	Inheritance	Gene defect
Fragile X	SJ	+	ARD/MVP	X linked	Unknown
Marfan's syndrome	SJB	-	ARD/MVP	Dominant	Unknown
Ehlers-Danlos syndrome	SJB	-	ARD/MVP	Dominant or recessive	Specific gene defect in some subgroups
Homocystinuria	JE	+	-	Recessive	Specific enzyme deficiency

ARD, aortic root dilatation; E, eyes; J, joints; MVP, mitral valve prolapse; S, skin.

ELECTROCARDIOGRAMS

One patient was in atrial fibrillation with a ventricular rate of 90/min (not on any medication). Two others, who were brothers, had sinus tachycardia with nodal bigeminal extrasystoles; another patient had sinus arrest with nodal escape beats. The remaining 19 electrocardiograms were normal.

ECHOCARDIOGRAPHY AND DOPPLER ULTRASOUND

In five patients (22%) cross sectional echocardiography showed mitral valve prolapse, and two also had mitral regurgitation on Doppler examination. No abnormality was shown in the two patients with isolated apical late systolic murmurs. Otherwise echocardiographic findings correlated well with auscultatory findings in that all four patients with clicks had echocardiographic prolapse, and both with clicks and murmurs had Doppler evidence of mitral regurgitation.

Twelve patients (52%) had dilated aortic roots, with the diameter being above the 95th centile for age and body surface area. There was no correlation between age and aortic root dimension. One patient had associated aortic regurgitation, and another had aortic valve stenosis and regurgitation. Four of these patients had mitral valve prolapse, two also had mitral regurgitation, and three had cardiomegaly on the chest x ray.

Discussion

Little is known about the life expectancy of patients with fragile X syndrome. Although they have cardiac abnormalities similar to those seen in patients with other types of connective tissue dysplasia, it is not clear whether the cardiac lesions are progressive or influence the prognosis.

Loehr *et al* examined 40 patients with fragile X syndrome.⁶ Twenty two (55%) had evidence of mitral valve prolapse diagnosed by both auscultation and M mode echocardiography; 80% of men over the age of 18 years had mitral valve prolapse. Their criteria for echocardiographic diagnosis of prolapse were not strictly defined. It may be that more stringent recent echocardiographic criteria have led

to fewer false positive diagnoses, thus explaining the lower frequency of mitral valve prolapse in our study. However, although we used a cross sectional echocardiographic definition of mitral valve prolapse, the frequency of abnormalities would have been no higher had we used M mode recordings alone.

Loehr *et al* found that only seven (20%) of 34 male patients had aortic root dilatation, but their patients were aged nine months to 31 years.⁶ We found a higher frequency of aortic root dilatation (52%), but the wide age range of our patients and the lack of correlation between age and aortic root dimension suggest that the lesion is not progressive.

The influence of these cardiovascular abnormalities is not known. None of our patients had symptoms and none had received antibiotic prophylaxis against infective endocarditis. We are not aware of any deaths related to cardiovascular disease or sudden unexplained deaths in our population of patients; but ours was not a longitudinal study. Although the similarities with Marfan's syndrome suggest that patients with fragile X syndrome are potentially at risk, it is not yet known whether these cardiac lesions carry the same risk of sudden death as in Marfan's syndrome.

Examination of our patients did not include detailed assessment of the joints, skin, or other physical manifestation of the syndrome but, in view of the extensive phenotypic heterogeneity, it would be interesting if any phenotypic pattern was shown to be consistently associated with mitral valve prolapse.

Patients with fragile X syndrome have a fragile site on the X chromosome. The gene responsible for the phenotype is probably related to the fragile site. Although a specific abnormality of connective tissue has not yet been shown, the prevalence of mitral valve prolapse and aortic root dilatation, together with some of the physical manifestations of the syndrome, suggest that there is an underlying connective tissue dysplasia, perhaps similar to that seen in Marfan's syndrome, Ehlers-Danlos syndrome, and homocystinuria (table). The precise relation between these conditions awaits definition of the basic biochemical defect in the fragile X and similar syndromes.

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Genetic evidence that mutations in the *COL1A1*, *COL1A2*, *COL3A1*, or *COL5A2* collagen genes are not responsible for mitral valve prolapse

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SUMMARY DNA markers were used to assess the segregation of genes encoding the collagen types that predominate in the mitral valve (types I, III, and V) in two family pedigrees that are phenotypically different but showed dominantly inherited mitral valve prolapse. The inheritance of these markers was compared with the segregation of the phenotype for mitral valve prolapse in both families. In one family it was shown that the *COL1A1*, *COL1A2*, *COL3A1*, and *COL5A2* genes segregated independently of the phenotype; in the other family the results for *COL1A1*, *COL1A2*, and *COL5A2* were similar but analysis at the *COL3A1* locus was not possible.

These data indicate that in these families mitral valve prolapse does not arise from a defect in one of these collagen genes.

Mitral valve prolapse is remarkably common. Its prevalence has been studied in women and men separately^{1,2} and in general surveys³⁻⁵ and estimates range from 5% to 15%. Mitral valve prolapse is inherited as an autosomal dominant trait and the gene shows incomplete penetrance with age and sex dependent expression.⁶ The major pathological changes include an increase of the cusp area with elongation or rupture of the chordae tendineae, resulting in prolapse of the valve into the left atrium during systole. The clinical presentation is variable—in many cases mitral valve prolapse is little more than an auscultatory abnormality, but in some patients complications arise.⁷

Quantitative cross sectional echocardiographic techniques have showed two different patterns of mitral valve abnormality in patients with mitral valve prolapse, and evidence suggested that these were associated with distinct phenotypic features and risks

of complications.^{8,9} These subtypes may reflect genetic heterogeneity within the mitral valve prolapse syndrome, and certain complications, such as chordal rupture, may be associated with specific mutations.

The pathogenesis of mitral valve prolapse is unknown. It is, however, a common manifestation of various systemic connective tissue disorders,³ for example some of the Ehlers-Danlos syndromes and Marfan syndrome, in which there is evidence of a collagen defect.¹⁰

Histologically the lesion is characterised by fragmentation of the collagenous bundles within the valve fibrosa.⁷ Several studies have implicated collagen defects as the primary events causing this abnormality, and mutations in collagen genes have been shown in some disorders that are associated with mitral valve prolapse.¹⁰ Collagen types I, III, and V predominate in the mitral valve and, with the exception of type III collagen which is the product of a single gene (*COL3A1*) located on chromosome 2, these proteins are encoded by more than one gene.¹¹ Type I is the product of two genes, *COL1A1* and *COL1A2*, located on chromosomes 17 and 7 respectively; type V is thought to be encoded by three

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genes, of which only one (*COL5A2* on chromosome 2) has been cloned.¹¹ Heterogeneity in mitral valve prolapse might reflect a variety of mutations affecting different genes which could determine the severity of the lesion, as is seen in osteogenesis imperfecta.^{10,12}

The use of DNA markers to study the inheritance of specific genes is now well established and has been successfully used to study various inherited diseases.¹³ These restriction fragment length polymorphisms are inherited as codominant traits and can be used as markers in segregation analysis. We studied collagen gene restriction fragment length polymorphisms in two families in which mitral valve prolapse was segregating as an autosomal dominant trait.

Patients and methods

SUBJECTS

Because prolapse is not uncommon all the members of each family were given a thorough physical examination and underwent M mode and cross sectional echocardiography to check for the possibility that mitral valve prolapse might also be present in a spouse. Standard criteria were used for the interpretation of the echocardiograms.^{14,15} Specifically, mitral valve prolapse was considered to be present when M mode tracings targeted on cross sectional echocardiography showed late systolic displacement of the continuous mitral leaflet interfaces by at least 2 mm behind the line between the points of valve closing and opening, or when systolic billowing of one or both leaflets across the mitral annular plane in systole was demonstrated in the parasternal long axis view.^{14,15} The apical four chamber view was not used because of recent evidence that apparent leaflet billowing in this view may be normal. Use of this view leads to false positive diagnosis of mitral valve prolapse because of the non-planar ("saddle") shape of the mitral annulus.¹⁶ The echocardiograms for both families were read by the same investigator (RBD) to exclude any variation in the definition of mitral valve prolapse.

RESTRICTION ENZYME ANALYSIS OF DNA

Genomic DNA was extracted from leucocytes contained in 10–20 ml of anticoagulated blood, as described previously.¹⁷ Samples of DNA were digested to completion by various restriction endonucleases, the fragments were separated electrophoretically on 1% agarose gels, and blotted on to nylon or nitrocellulose support membranes according to established protocols.¹⁸

COLLAGEN GENE RESTRICTION FRAGMENT LENGTH POLYMORPHISMS

Polymorphisms associated with the genes encoding

the pro- α 1 and pro- α 2 chains of type I (*COL1A1* and *COL1A2*), pro- α 1 chain of type III (*COL3A1*), and pro- α 2 chain of type V (*COL5A2*) collagen were used in these studies. Variation at the *COL1A1* locus was detected in *MspI* and *RsaI* digests using the genomic probes p1A1H17526 and p2FC6 respectively.¹⁹ For *COL1A2*, an *EcoRI* polymorphism was detected with a 6.75 kb genomic clone NJ3²⁰ and an *RsaI* marker was visible with the cDNA Hf32.²¹ For the *COL5A2* gene, an *MspI* polymorphism²² was used and detected with a 3.5 kb genomic clone, DMC2. Two polymorphic markers were used for the *COL3A1* gene, both located in the 3' untranslated region: one was detected by *AvaII* and the cDNA probe pIII-33²³ and the other by *EcoRI* with a 2.1 kb fragment of genomic clone IdF17.²⁴

To estimate the likelihood that a marker was linked to the mutant locus we calculated the ratio of the probability for that association at a given genetic distance (the recombination fraction, θ) to the probability of association at a distance where the two are not linked ($\theta = 0.5$)—that is where the association could have arisen by chance alone. This ratio is usually expressed as a logarithm, the lod (log of odds) score for linkage. A lod score of 3 or greater indicates odds of 1000:1, or better, in favour of linkage and is taken as formal proof of linkage. Conversely lods of -2 or more are taken to indicate exclusion.

LINKAGE ANALYSIS

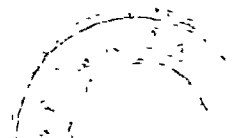
These calculations were performed by the computer program LINKAGE,²⁵ and we took into account the incomplete penetrance and variable sex dependent expression of the phenotype. A gene frequency based on a 5% population prevalence was used, together with estimates of 50% penetrance for males and 90% for females, based on the data of Devereux *et al.*^{6,15} No data were available to show what proportion of young unaffected individuals develop mitral valve prolapse later on in life and, therefore, no allowance could be made for age dependant expression.

Results

CLINICAL SUMMARIES

Quantitative echocardiographic methods were not used in these studies and, therefore, no conclusive distinction between different subtypes of mitral valve prolapse could be made.

Family H—The figure shows the pedigree of this three generation family. Of the five siblings in the second generation, two (II.3 and II.7) had clear mitral valve prolapse shown by echocardiography and a third (II.5) showed signs of slight prolapse. No information was available on the clinical state of the



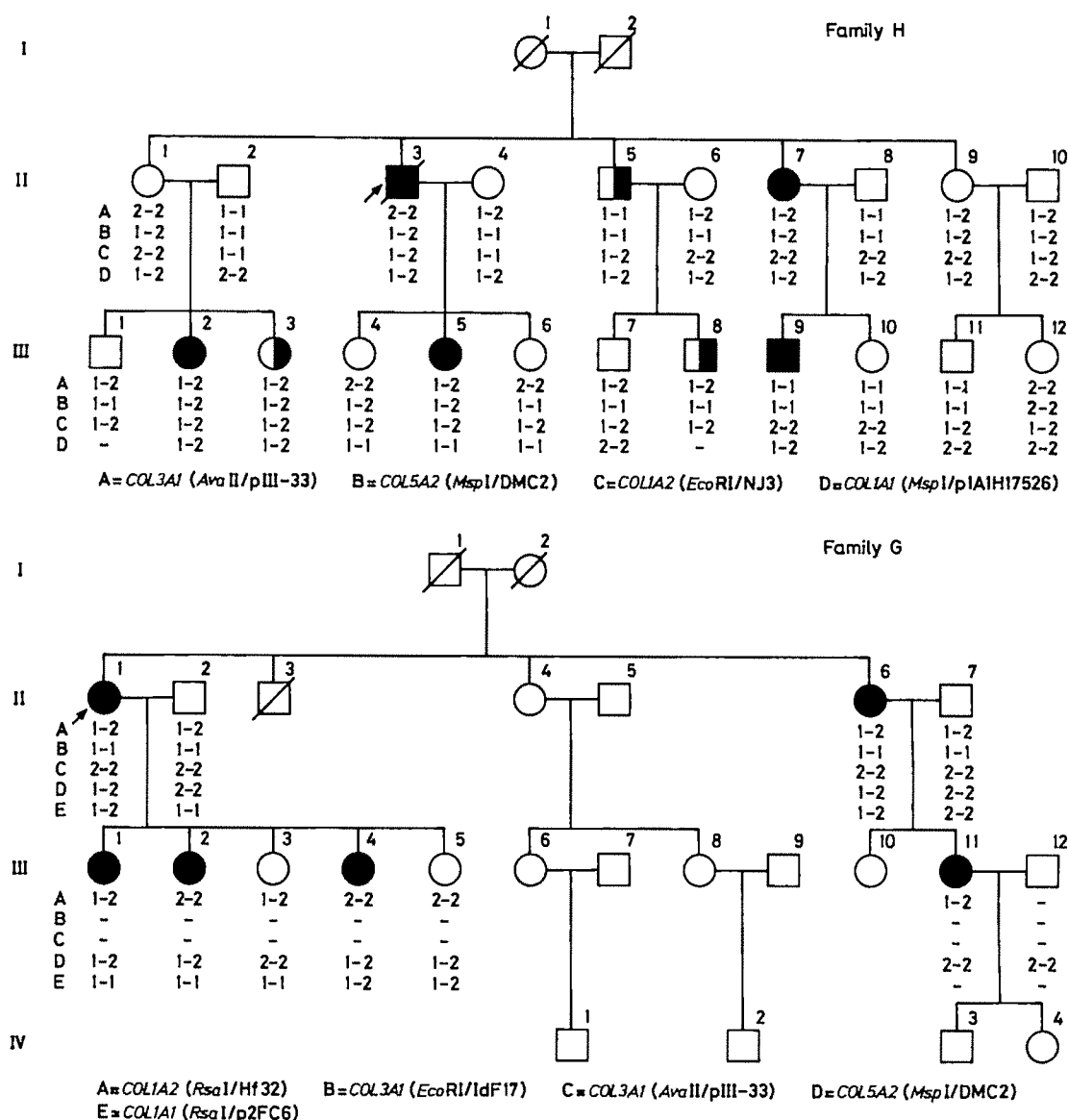


Figure Pedigrees of two families showing the segregation of the mitral valve prolapse phenotype. Circles denote females, squares are males, and black symbols identify affected individuals. Half shaded symbols indicate mild prolapse. The genotypes for each of the collagen genes are listed under each individual and are identified by the appropriate key.

two individuals in the first generation. The proband had undergone surgery to replace his mitral valve after rupture of chordae to both the anterior and posterior cusps. He has since died. In addition, there were other manifestations in this pedigree that are characteristic of connective disorders (table 1). In the second generation, three of the five siblings had increased armspan-height differences (II.3,

+13.5 cm; II.5, +6.3 cm; II.7, +9.0 cm), all five had early onset varicose veins severe enough to require operation, and three (II.3, II.5, and II.7) had hyperextensible skin. Of the 12 individuals in the third generation, three had mitral valve prolapse shown by echocardiography (III.2, III.5, and III.9) and in two others (III.3 and III.8) the echocardiograms suggested a degree of prolapse. One of those

Table 1 Description of phenotypes seen in the two families

	Armspan* -height (cm)	JHS	Echo	Auscultation	Skeletal†	Vascular‡	Skin§
Family H:							
II. 1	3.0	0	—	—	—	+	—
II. 3	13.5	0	Valve replaced	—	—	+	+
II. 5	6.3	0	±	—	—	+	+
II. 7	9.0	1/9	+	+	—	+	+
II. 9	3.5	1/9	—	—	—	+	—
III. 1	ND	0	—	—	—	—	—
III. 2	6.0	0	+	+	+	—	—
III. 3	2.0	6/9	±	—	—	—	+
III. 4	3.2	0	—	—	—	—	—
III. 5	5.0	0	+	—	—	—	—
III. 6	2.5	0	—	—	—	—	—
III. 7	3.0	3/9	—	—	—	—	—
III. 8	3.0	0	±	—	—	—	—
III. 9	1.0	0	+	—	—	—	—
III.10	-2.5	0	—	—	—	—	—
III.11	7.5	0	—	—	+	—	—
III.12	3.0	2/9	—	+	—	—	—
Family G:							
II. 1	7.8	N/A	—	—	—	N/A	—
II. 2	0.0	N/A	+	+	—	N/A	—
II. 4	N/A	N/A	—	—	—	N/A	N/A
II. 6	-5.0	N/A	+	+	—	N/A	—
II. 7	5.0	N/A	±	—	—	N/A	—
III. 1	-4.0	N/A	+	—	+	N/A	—
III. 2	1.0	N/A	+	—	—	N/A	—
III. 3	1.0	N/A	+	+	—	N/A	—
III. 4	4.0	N/A	+	+	—	N/A	—
III. 5	1.0	N/A	±	—	—	N/A	—
III.10	N/A	N/A	—	—	—	N/A	N/A
III.11	-0.5	N/A	+	+	+	N/A	N/A
III.12	N/A	N/A	—	—	N/A	N/A	N/A
IV. 3	6.5	N/A	—	—	—	N/A	—
IV. 4	4.0	N/A	—	—	—	N/A	—

*A difference of >7.5 cm was regarded as clinically significant. JHS, joint hypermobility score calculated as described by Beighton and Horan.²⁴ ± denotes a suggestion of prolapse that does not fully satisfy diagnostic criteria. †+ = kyphosis, scoliosis, or pectus deformities. ‡Early onset varicose veins. §Evidence of hyperextensible skin. N/A, not available.

mildly affected (III.3) also had excessively hypermobile joints and hyperextensible skin. Skeletal defects were present in two individuals: III.2 had an increased armspan-height difference (+6.0 cm), kyphosis, and pectus excavatum, while III.11 also had abnormally long arms (+7.5 cm), kyphosis, and scoliosis. The vascular manifestations seen in the parents were not obvious in their offspring.

Family G—There was no information on the first generation of this family (fig). Of the four siblings in the second generation, two of the three who were available for examination were affected (II.1 and II.6), and one of them (II.1) has a history of cerebrovascular disease. No information was available on the clinical state or genotype of the dead brother. The nuclear family of an unaffected sibling (II.4) was not studied. All the offspring in the third generation were female; four of them were clearly affected. Two siblings had mild mitral valve prolapse: III.3 showed a suggestion of prolapse on one echocardiogram and met diagnostic criteria in a second study, but was normal on auscultation. She had mild left ventricular dysfunction and electrocar-

diographic changes consistent with a previous episode of myocarditis, which could explain the positive echocardiogram. Her sister III.5 was completely normal on first examination, but four years later an echocardiogram showed slight evidence of prolapse and there was a discernible systolic murmur with a possible click. In the absence of firm evidence showing mitral valve prolapse, this individual was regarded as normal for the purposes of these analyses. In the fourth generation, the two siblings studied were normal. Two individuals with mitral valve prolapse in this family had mild scoliosis; no one with prolapse had an armspan-height difference of more than 7.5 cm and none had hyperextensible skin (table 1).

GENETIC ANALYSIS

The genotypes for each of the collagen loci are listed below each individual in the two pedigrees presented in the figure, and table 2 shows the calculations of the lod scores for each locus at various recombination distances.

In family H, exclusion of the *COL1A1* gene is

Table 2 Lod scores for the collagen loci calculated at various recombination fractions

Family	Locus	Recombination fraction (θ)									
		0	0.05	0.10	0.15	0.20	0.25	0.30	0.35	0.40	0.45
G	COL1A1	-0.74	0.03	0.12	0.17	0.17	0.14	0.10	0.07	0.03	0.01
H	COL1A1	-1.44	-0.81	-0.53	-0.35	-0.23	-0.14	-0.09	-0.08	-0.02	-0.005
G	COL5A2	-1.09	-0.99	-0.79	-0.57	-0.40	-0.26	-0.16	-0.09	-0.04	-0.01
H	COL5A2	-4.24	-1.91	-1.12	-0.68	-0.41	-0.23	-0.12	-0.05	-0.02	-0.001
G	COL1A2	-0.62	-0.41	-0.28	-0.19	-0.13	-0.08	-0.05	-0.03	-0.01	-0.002
H	COL1A2	-3.24	-1.23	-0.74	-0.48	-0.31	-0.20	-0.12	-0.06	-0.03	-0.01
G	COL3A1	Not informative									
H	COL3A1	-1.90	-1.22	-0.80	-0.54	-0.36	-0.23	-0.14	-0.08	-0.03	-0.01

explained as follows. The proband (II.3) is heterozygous 1-2 and has an affected child who is homozygous for the 1 allele, ruling out an association with the 2 allele. The 1 allele is also excluded because the homozygous affected individual III.5 has unaffected siblings with the same genotype, and their affected cousin III.2 has inherited the 1 allele from her unaffected mother (lod score -1.44 at $\theta = 0$). The COL1A2 locus was also excluded. The proband has a genotype of 1-2 for the COL1A2 locus and he has passed the 2 allele on to all three of his daughters, only one of whom is affected. This effectively excludes the involvement of the 1 allele. Three of his siblings (II.1, II.7, and II.9) were homozygous 2-2, but only one was affected, suggesting that this allele is also not involved (lod -3.24 at $\theta = 0$). This could be due to incomplete penetrance of the gene, but the exclusion of the 2 allele is based on the fact that the mildly affected heterozygote III.8 inherited the 2 allele from his unaffected mother and not from his father. Similarly, in the COL5A2 analysis, the heterozygous proband passed the 2 allele on to two of his daughters, of whom only one was affected. This could be due to incomplete penetrance, but the presence of the homozygous 1-1 affected cousin (III.9), excludes linkage. The inheritance of the 1 allele by the affected daughter (III.5) from her mother (II.4) and not her affected father (III.3) excludes linkage of the trait to this locus (lod -4.24 at $\theta = 0$). Therefore, tight linkage has been excluded at the COL1A1, COL1A2, and COL5A2 loci in this family. In the COL3A1 analysis, two affected individuals were homozygous for the 1 (III.9) or 2 (II.3) allele. A lod score of -1.9 at $\theta = 0$ for this analysis strongly suggests exclusion at this locus. Although this does not quite achieve the score that is accepted as formal proof of exclusion (lod -2.0), the trait is clearly not cosegregating with the COL3A1 locus.

No analysis at the COL3A1 locus was possible in family G, as the individuals in generation II were all homozygous for both restriction fragment length polymorphisms and consequently were not infor-

mative. Linkage to the COL5A2 locus was excluded on the basis that the three affected heterozygous sisters (III.1, III.2, and III.4) inherited the 1 allele from their affected mother, but the presence of the homozygous 2-2 affected cousin (III.11) rules out the involvement of this allele. The 2 allele is excluded because the three affected daughters of the proband (III.1, III.2, and III.4) inherited the 1 allele from their mother and not the 2 allele (lod score -1.09 at $\theta = 0$). We also showed discordance with the COL1A1 locus. The homozygous affected individuals III.1 and III.2 inherited the 1 allele from their affected mother, ruling out linkage to the 2 allele; but the affected individual III.4 inherited the 2 allele from her mother and not the 1, excluding linkage with this allele as well (lod -0.74 at $\theta = 0$). For COL1A2, the mitral valve prolapse locus could not be linked to the 1 allele because there are affected individuals homozygous for the 2 allele (III.2 and III.4). Exclusion of the 2 allele is based on the unaffected individual III.5 who is homozygous 2-2, as are her affected sisters III.2 and III.4 (lod -0.62 at $\theta = 0$). It has been shown that the mitral valve prolapse gene is not completely penetrant and its expression varies with age and sex,⁶ so this exclusion cannot be certain. Although these data do not provide any evidence to support linkage of the phenotype with any of these loci, the lod scores in family G do not reach the value (-2.0) that is required for formal statistical proof of exclusion.

Discussion

Mitral valve prolapse is a common feature of various inherited connective tissue disorders in which collagen defects have been described.³ This association taken together with histological evidence of an abnormal collagenous matrix^{5,7} supports the view that abnormal collagen could be involved in the aetiology of mitral valve prolapse. Data from various studies on isolated valves that show a reduction or absence of type III collagen in the tissue,²⁷ abnormally high rates of collagen synthesis,²⁸ and increased

collagen production²⁹ are also consistent with this hypothesis. Additionally, in the family of a proband with clinically diagnosed Ehlers-Danlos type IV syndrome, mitral valve prolapse was clearly associated with abnormal synthesis of type III collagen.³⁰ Thus there is evidence favouring the involvement of a collagen defect, perhaps of type III collagen specifically, in the pathogenesis of mitral valve prolapse.

A rapid method for testing the hypothesis that mitral valve prolapse arises from a heritable collagen gene defect is available through the use of collagen gene polymorphisms and segregation analysis in affected families. Because the markers are so closely associated with the genes in this particular case they are ideal for use in segregation analysis because the probability of a crossover occurring between marker and gene in any given meiosis is extremely small. Thus any examples of discordance between the candidate gene and the abnormal phenotype effectively exclude that gene as the mutant locus.

In sequential studies of 45 and 48 patients with mitral valve prolapse who had 179 and 171 first degree relatives respectively it was shown that mitral valve prolapse was transmitted in an autosomal dominant fashion, that its expression was dependant on age and sex, and that the gene showed incomplete penetrance.^{6,15} These points complicate the analysis of genetic linkage. For example, exclusions based on unaffected individuals in a particular kindred can never be certain, even if age based probability curves are available. This problem arose in the exclusion of one of the *COL1A2* alleles in family G and also in the exclusion of one of the *COL1A1* alleles in family H. The woman (III.5) in family G was assessed as normal when she was first examined. But four years later there was slight echocardiographic evidence of prolapse, a late systolic murmur, and possibly a midsystolic click. Her electrocardiogram was normal and she had no symptoms. Because she is younger (27) than her two homozygous affected sisters (40 and 30) prolapse could develop later. But, as her exact clinical state was uncertain and there was no clear indication of mitral valve prolapse, she was regarded as normal. In the case of family H, the *COL1A1* 1 allele was excluded because two homozygous siblings (III.4 and III.6) were unaffected and one of them was three years older than her affected sister. It may be that mitral valve prolapse will develop later in these individuals, so exclusion cannot be certain. However, the presence of an affected heterozygous cousin III.2 who has inherited the 1 allele from her unaffected mother adds weight to the argument because, with an estimated penetrance of 90% for females,^{6,15} at the age of 55 the mother should have shown signs of prolapse if it were going to develop. These con-

clusions are supported by the negative lod scores calculated for these loci (table 2), although in neither case do the genes achieve the -2.0 score that is taken as formal proof of exclusion. Because this is a segregation analysis of candidate genes rather than random markers, a single recombinant or negative lod score at zero recombination distance is sufficient to exclude the candidate locus.

Phenotypic heterogeneity has been established within the mitral valve prolapse syndrome, and two separate patterns of prolapse could be defined by quantitative cross sectional echocardiography.³¹ One of these patterns of prolapse was associated with a distinct habitus that included low body weight and bony abnormalities of the thorax, which could reflect an underlying mild defect in systemic connective tissue. Although mitral valve prolapse was segregating as an autosomal dominant trait in both families in this study, the two were clearly phenotypically different. Family H showed various abnormal systemic features whereas G did not, indicating the possibility that each family reflected a separate subtype. These two families were assessed at different centres and, although this did not affect the diagnosis of mitral valve prolapse by standardised echocardiographic methods and a single experienced investigator reviewing the studies, it was not possible to apply the quantitative echocardiographic techniques used by Pini *et al.*^{8,9} to family H to verify whether or not these two families did reflect heterogeneity of mitral valve prolapse.

The manifestations seen in family H were consistent with features observed both in Ehlers-Danlos syndrome (varicose veins, hyperextensible skin, and joint hypermobility) and in the Marfan syndrome (abnormally long arms and pectus deformity). Biochemical analysis of the resected valve from the proband showed abnormal type III/III + I collagen ratios, but it was probable that this was due to the development of secondary fibrosis on the valve, rather than an inherent deficiency in the expression of one of these collagen types.³¹ The segregation analysis confirms the fact that the trait is not linked to the *COL1A1*, *COL1A2*, *COL3A1*, or *COL5A2* loci. That is to say mitral valve prolapse in this family was not caused by a structural defect in any of these collagen genes. In contrast, family G seemed not to have any signs of a generalised connective tissue deficiency, but did have systolic billowing of the mitral leaflets in a qualitative evaluation of cross sectional echocardiograms. This pattern of prolapse coupled with the absence of any systemic signs (table 1) suggests that this family may represent "type I" mitral valve prolapse as defined by Pini *et al.*^{8,9} No biochemical data were available for this family, but again there was no evidence to support linkage of

mitral valve prolapse to three of the four collagen loci studied. It is possible that the trait could be caused by a defect in the *COL3A1* gene, because the family was not informative for either of the polymorphisms at this locus, and it will be restudied as and when new *COL3A1* gene polymorphisms are found.

It has been suggested that a collagen abnormality is responsible for the Marfan syndrome.³² Studies on Marfan syndrome pedigrees, however, also failed to establish an association for this disorder with the major fibrillar collagen genes,^{33,34} and mitral valve prolapse is frequently seen in patients with this disorder. It was suggested that other genes coding for extracellular matrix components are possible candidates for the Marfan phenotype,³⁵ and this could be equally likely for mitral valve prolapse. An alternative hypothesis is that mitral valve prolapse is a polygenic disorder, where the phenotype arises from the interaction of more than one gene, and the individual genes responsible cannot be identified because alone they do not cause major changes in the phenotype.³⁵ It is also feasible that an error in the enzymes responsible for the complex post-translational processing of collagen could be responsible for the formation of a valve with a weakened extracellular matrix, leading eventually to mitral valve prolapse. But this seems to be unlikely because enzyme deficiencies are generally recessive traits, although a few are dominantly inherited.

Therefore, despite the biochemical and clinical evidence implicating collagen, it seems that mitral valve prolapse in these families does not arise from a defect in the structural collagen genes that we studied. The remaining type V collagen genes for which probes are not yet available remain potential candidates, as do the genes encoding other components of the connective tissue matrix such as elastin and proteoglycans.

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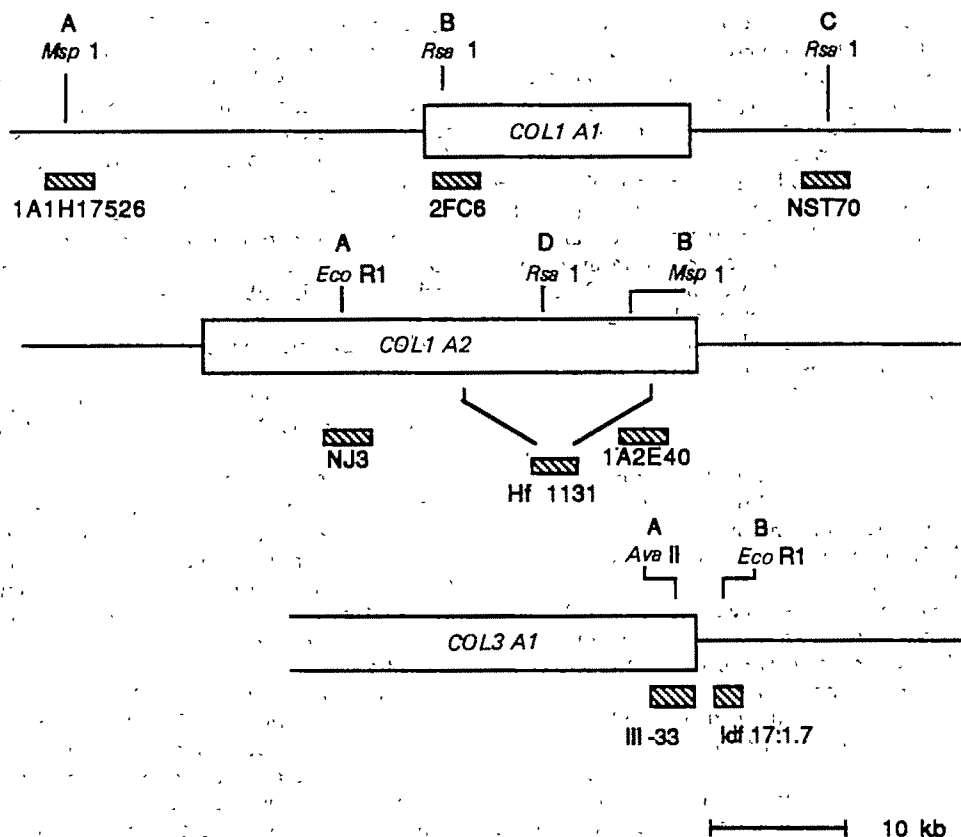


Fig 1 Map of the segregation marker systems at COL1A1, COL1A2, and COL3A1.

echocardiography recordings were made from the parasternal long axis and the apical four chamber views.

Pedigree 1

Propositus II.2—A 39 year old man with a known family history of mitral valve prolapse underwent emergency mitral valve replacement because of worsening congestive heart failure in the presence of a recent pansystolic murmur. Although he had had a heart murmur since birth he had been symptom free until a few years ago when he first experienced recurrent episodes of palpitation and mild chest pain unrelated to exercise. He made a good recovery.

Pedigree 2

Propositus III.5—A 19 year old man presented with a history of recurrent episodes of palpitation. The physical examination was entirely normal except for a late systolic click followed by a murmur heard over the mitral area. Echocardiographic examination showed considerable elongation of the anterior mitral valve leaflet and a mobile cystic mass that seemed to

be continuous with its tip. The findings in this case have been described elsewhere.²⁴

Pedigree 3

Propositus III.2—A 29 year old man presented with a history of atypical chest pain and palpitation. A late systolic click and murmur were heard over the apex. The physical examination was otherwise unremarkable. The echocardiographic examination showed similar appearances to those seen in pedigree 2.

Table 1 summarises the clinical, auscultatory, and echocardiographic findings in the affected family members. Relatives scored as unaffected were normal for all variables tested.

ASSIGNMENT OF GENOTYPE

DNA was prepared from peripheral blood taken into edetic acid. Restriction enzyme digestion and agarose electrophoresis blotting on to nitrocellulose filters followed our modifications of standard protocols.²⁵ Hybridisation probes (fig 1) were labelled with ³²P by either nick translation or random primer directed

Table 2 Haplotype notations at COL1A1, COL1A2, and COL3A1

Marker Enzyme Probe Reference	COL1A1		
	A <i>Msp</i> 1 1A1H17526 26	B <i>Rsa</i> 1 2FC6 26	C <i>Rsa</i> 1 NST70 27
Haplotype			
1	+	+	+
2	+	+	+
3	+	+	+
4	+	+	+
5	+	+	+
6	+	+	+
7	+	+	+
8	+	+	+
Marker Enzyme Probe Reference	COL1A2		
	A <i>Eco</i> R1 NJ3 28	B <i>Msp</i> 1 1A2E40 29	D <i>Rsa</i> 1 Hf1131 30
1	+	+	+
2	+	+	+
3	+	+	+
4	+	+	+
5	+	+	+
6	+	+	+
7	+	+	+
8	+	+	+
Marker Enzyme Probe Reference	COL3A1		
	A <i>Ava</i> II pIII-33 31	B <i>Eco</i> R1 IdF17:1.7 32	
1	+	+	
2	+	+	
3	+	+	
4	+	+	

synthesis. Hybridisations were carried out overnight at 42°C in a mixture containing 50% v/v formamide, 5% w/v dextran sulphate, and 200 µg/ml heparin after prehybridisation of the filter overnight with the same mixture without dextran sulphate.

Three restriction site dimorphisms at both COL1A1,^{26,27} COL1A2²⁸⁻³⁰ and two at COL3A1^{31,32} were used as genetic linkage markers. Figure 1 shows the positions of the markers on the physical gene maps. Use of these three markers distinguished eight haplotypes at both COL1A1 and COL1A2 with four possible combinations allowed at COL3A1. Table 2 shows the notations of markers at the three loci. Where it was relevant to the analysis we confirmed paternity or maternity by means of the minisatellite probe 15.1.11.4.³³

Results

Figure 2 shows the genotypes at the three loci and table 3 summarises the results. Discordance between markers and mitral valve prolapse was seen in the pedigrees as follows.

Pedigree 1

COL1A2—Both II.2 and II.4 have inherited the gene for mitral valve prolapse from their mother I.2 but different COL1A2 alleles.

COL1A1 and COL3A1 markers at both loci were both non-informative because I.2 was homozygous in each case so the alleles could not be distinguished.

Pedigree 2

COL1A1—III.2 and III.3 both inherited the gene for mitral valve prolapse from their mother II.5 but different COL1A1 alleles.

COL1A2—Both II.4 and III.2 are double heterozygotes for COL1A2 markers. This means that they could have one of two possible genotypes 1-4 or 2-3 though examination of the pedigree shows that both individuals must have the same genotype. Consider the case where II.4 and III.2 have genotype 1-4 at COL1A2. In this case, III.2 must have inherited allele 4 from her father and allele 1 from her mother. However, III.3 must have inherited allele 1 from her father and allele 2 from her mother. So the two daughters have received different COL1A2 alleles from their mother but both have inherited the gene for mitral valve prolapse. Much the same argument applies if both II.4 and III.2 have genotypes 2-3. In this case II.5 has passed allele 2 to her daughter III.2 and allele 1 to III.3 but the gene for mitral valve prolapse to both.

COL3A1—II.5 is homozygous for COL3A1 markers so the pedigree is not informative.

Individual II.1, who was not examined, was reported to have been turned down for army selection because of a heart murmur. This raises the possibility that the gene for mitral valve prolapse is present in his sibs, one of whom is II.4, the father of the affected individuals in generation III. II.4 was thoroughly examined and no signs of mitral valve prolapse were seen by careful auscultation or echocardiography.

Pedigree 3

COL1A1—III.5 carries the gene for mitral valve prolapse but has no COL1A1 allele in common with either his two brothers III.2 and III.3 or his niece IV.2, all of whom also carry the gene for mitral valve prolapse.

COL1A2—III.2 and III.3 are both affected but have no COL1A2 alleles in common.

COL3A1—Consider III.7 and III.8. Both are affected but have inherited different COL3A1 alleles from their father.

Discussion

Several factors complicate linkage analysis in disorders such as mitral valve prolapse. First, it is a

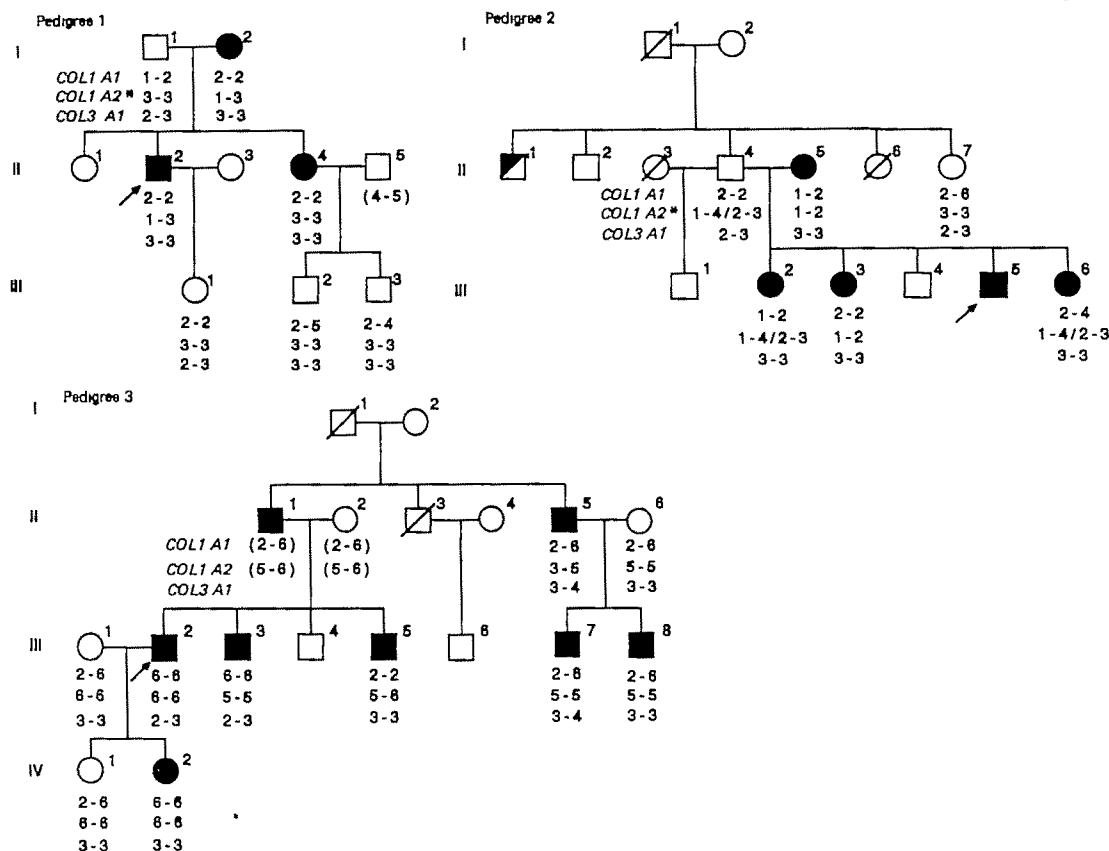


Fig 2 Three pedigrees showing mitral valve prolapse with collagen genotypes are shown in table 1. Black symbols are individuals scored as affected, white symbols are individuals who did not show symptoms of mitral valve prolapse. Proposits are arrowed. The partly shaded symbol indicates an individual II.1 in pedigree 2 who was not examined but was turned down by the army because of a "heart murmur". In pedigrees 2 and 3, the COL1A2* haplotypes are incomplete and are as follows: 1 = A + B +; 2 = A + B -; 3 = A - B +; 4 = A - B -. Deduced genotypes are shown in parentheses.

common disorder so that sibships may receive mitral valve prolapse genes from both parents. Second, the penetrance is incomplete. This makes analysis based on unaffected individuals more uncertain than in fully penetrant disorders because there is a high probability that they may have inherited the gene

without its expression being detected in the phenotype despite very careful examination. Third, it is not clear that mitral valve prolapse is always inherited so that there is a possibility that individuals in a pedigree scored as affected may not have received the mutant gene but are phenocopies for an unrelated reason.

Bearing these important considerations in mind we showed that neither of the two genes encoding the subunits of collagen I segregated with the mitral valve prolapse phenotype in two pedigrees in which the disorder appeared to be behaving as an autosomal dominant mendelian trait. In a third pedigree we excluded one of the genes, COL1A2, but not the other. Largely because of a lack of useful markers at COL3A1, we have only been able to analyse the segregation of this locus in one pedigree and this analysis showed discordance.

Table 3 Segregation of COL1A1, COL1A2, and COL3A1 in three pedigrees showing mitral valve prolapse

Pedigree	Locus		
	COL1A1	COL1A2	COL3A1
	NI	DS	NI
	DS	DS	DS
	DS	DS	DS

NI, non-informative; DS, discordant.

There are several reasons why we are cautious about interpretation of these results, but we can discount the probability of recombination between the markers at the loci and the physical limits of the gene. The maximum distance between markers is 50 kb which, barring unusually high recombination rates at the loci, translates to a crossover frequency of about 0.0005 per meiosis. This is insignificant compared with the other potential sources of error.

This study can only be regarded as preliminary and needs to be extended to larger pedigrees in which the segregation of the disease as an autosomal dominant trait is clearer and discordance can be demonstrated in several meioses. Nevertheless, this study suggests that the primary gene locus for mitral valve prolapse is not linked to either of the two collagen I loci nor, probably, to the collagen III locus. If this is the case then mutations in these genes cannot be the cause of the disease.

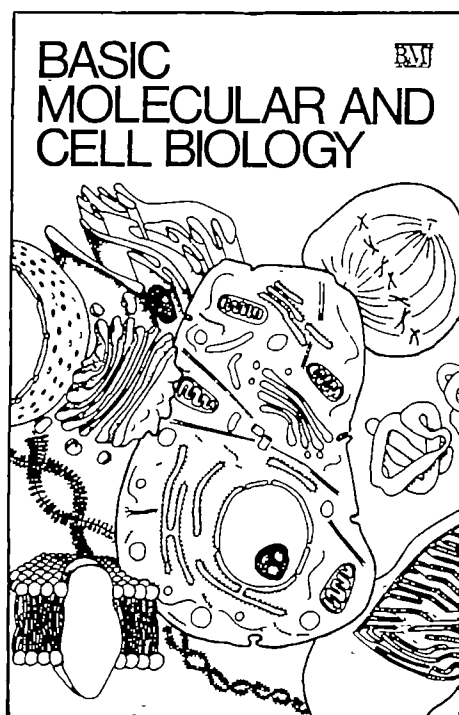
We thank the patients and their physicians who took part in this study especially Dr J Walker for echocardiography of pedigree 1. We are grateful to Dr F Ramirez for COL1A2 probes NJ3 and Hfl 131, to Dr R Dalglish for COL3A1 probes pIII-33 and IdF 17:1.7, and to Dr A Jeffreys for minisatellite probe 15.1.11.4. We thank the Arthritis and Rheumatism Council, Action Research for the Crippled Child, and the Medical Research Council for support.

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Case report

Acute myocardial infarction in infancy: unmasking of anomalous origin of the left coronary artery from the pulmonary artery by ligation of an arterial duct

NARAYANSWAMI SREERAM, STEWART HUNTER, CHRISTOPHER WREN

From the Department of Paediatric Cardiology, Freeman Hospital, Newcastle upon Tyne

SUMMARY Myocardial infarction and left ventricular failure developed within hours of ligation of a large arterial duct in a four week old infant. Anomalous origin of the left coronary artery from the pulmonary artery was confirmed by echocardiography. Despite emergency translocation of the anomalous coronary artery the patient died.

Anomalous origin of the left coronary artery from the pulmonary artery is a rare cause of heart failure in infancy. It is usually an isolated abnormality, although association with a persistent arterial duct has been reported.^{1,2} We describe an infant who developed acute left ventricular failure within hours of ligation of a large duct.

Case report

A four week old female infant was admitted with a history of poor feeding. She had been delivered at 35 weeks' gestation (birth weight 2 kg) by caesarean section because of maternal pre-eclampsia and she had been well until 48 hours before admission.

On admission she had the classic signs of a large arterial duct with cardiac failure. The chest x ray showed cardiomegaly and pulmonary plethora. The electrocardiogram showed sinus rhythm, with ST segment depression in leads V2-V6 (fig). Cross sectional echocardiography confirmed a large duct and showed left atrial enlargement.

Because there was no improvement with medical treatment, the duct was ligated. The patient was extubated four hours after the operation but appeared unwell with tachypnoea and tachycardia and required re-intubation. A repeat chest x ray showed persisting cardiomegaly and pulmonary ven-

ous congestion. Cross sectional and colour Doppler echocardiography showed a slightly dilated, dyskinetic left ventricle, with mitral valve regurgitation. The patient was treated with infusions of dobutamine and glyceryl trinitrate.

Repeat cross sectional and colour Doppler echocardiography after 48 hours showed deteriorating ventricular function, worse mitral regurgitation, and identified an anomalous origin of the left coronary artery from the left posterior aspect of the main pulmonary artery. An electrocardiogram showed deep Q waves in leads I, aVL, and V6 associated with ST segment elevation and T wave inversion (fig). Emergency translocation of the left coronary artery was undertaken. Extensive infarction of the left ventricle was seen at operation. The origins of the circumflex and left anterior descending arteries were found to be separate but immediately adjacent and they were transferred from the pulmonary artery to the aorta. Cardiopulmonary bypass could not be discontinued because of left ventricular failure, and the patient died.

Discussion

Anomalous origin of the left coronary artery from the pulmonary artery is rare. Because it usually presents with myocardial infarction in infancy, electrocardiographic diagnosis is often straightforward although echocardiographic confirmation may be difficult.³ Prospective diagnosis, before myocardial infarction has occurred, is unlikely to be possible.

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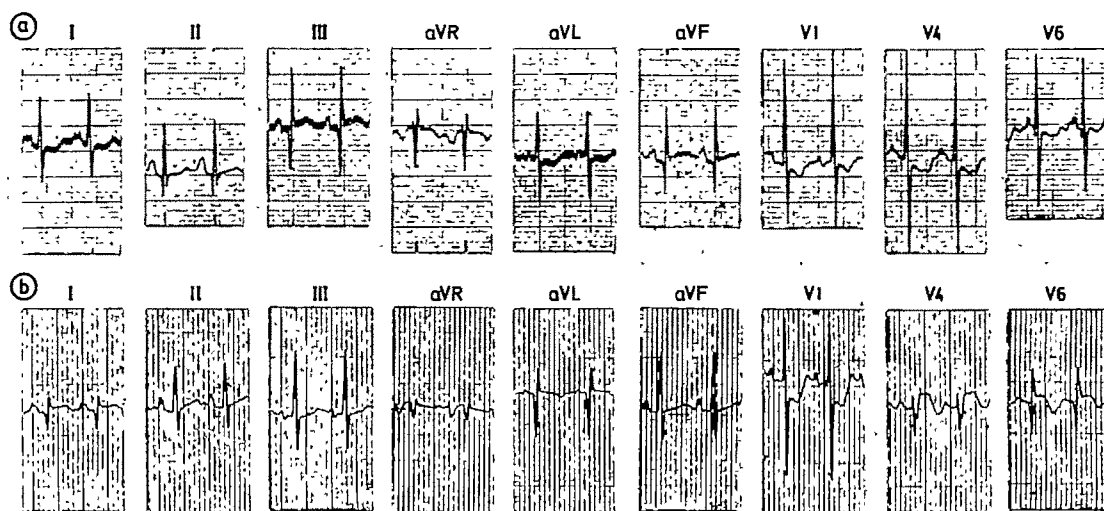


Fig (a) Preoperative electrocardiogram showing ST segment depression in anterolateral leads. (b) An electrocardiogram recorded 48 hours after operation showing acute transmural anterolateral infarction with new Q waves in leads I, aVL, and V6 and ST segment elevation in I, V4 and V6.

In the fetus and in the neonate with physiological pulmonary hypertension the perfusion pressure in the anomalous coronary artery is normal. As the pulmonary artery pressure falls after birth, left coronary perfusion is reduced, causing ischaemic myocardial damage that usually presents as congestive heart failure after two or three months. The age of onset of symptoms varies depending on the rate of fall of pulmonary artery pressure and the development of collateral connections with the right coronary artery. A large arterial duct will maintain adequate left coronary artery perfusion and thus delay presentation until the duct is ligated.

Ortiz *et al* reported a one year old child in whom cardiac failure developed two months after ligation of a large duct.¹ Anomalous origin of the left coronary artery from the pulmonary artery was diagnosed two

years later. Clinical deterioration may, however, be acute, as shown by the progression of events in our patient.

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Notices

Coronary arteriography

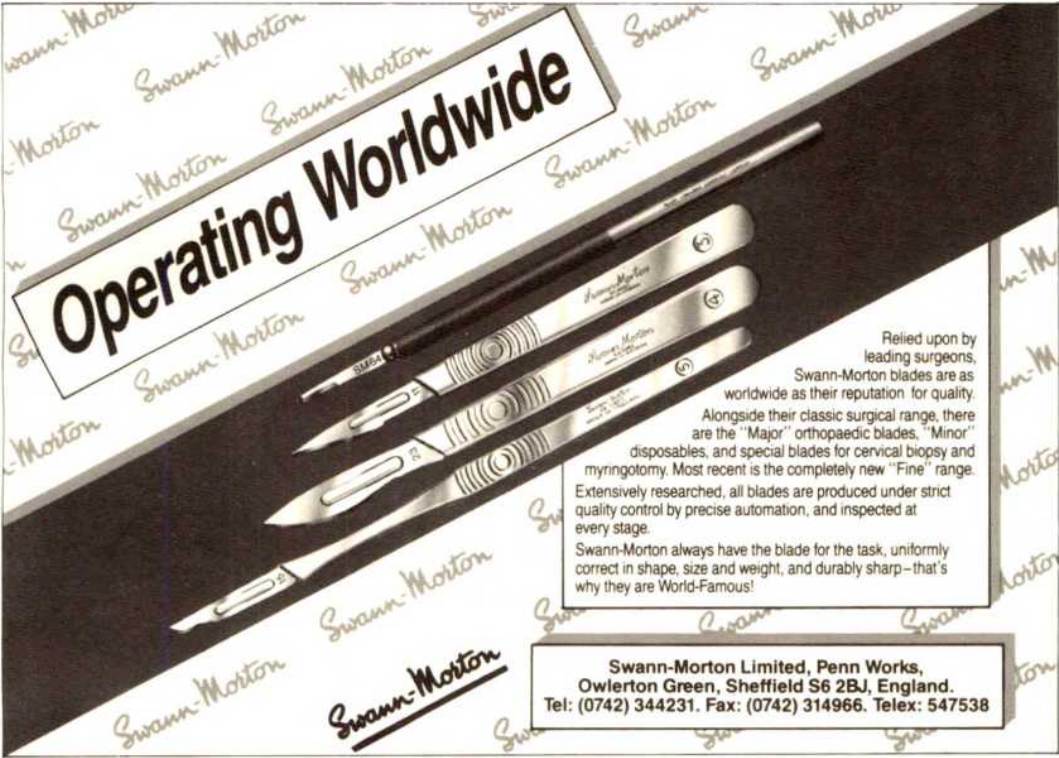
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